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Global Clinical Development - General Medicine

LCZ696/Entresto®

Clinical Trial Protocol CLCZ696B2320 / NCT02884206

A multicenter, randomized, double-blind, active-controlled study to evaluate the effects of LCZ696 compared to valsartan on cognitive function in patients with chronic heart failure and preserved ejection fraction

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List of abbreviations

Aβ	Amyloid beta
ACE(i)	Angiotensin converting enzyme inhibitor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease assessment scale-cognitive subscale
ADNI	Alzheimer's disease neuroimaging initiative
AE	Adverse event
AESI	Adverse event of special interest
Alb	Albumin
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APOE4	Apolipoprotein E ε4 allele
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AST	Aspartate aminotransferase
AUC	Area under the curve
bid	twice daily dosing
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CCB	CogState cognitive battery
CFR	US Code of Federal Regulations
CI	Confidence interval
Cmax	Concentration maximum
CNS	Central nervous system
COX	Cyclo-oxygenase
CPAL	Continuous paired associate learning
CPO	Country pharma organization
CQA	Compliance quality assurance
CRF	Case report form
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicidality severity rating scale
CV	Cardiovascular
DAR	Drug administration record
DBP	Diastolic blood pressure
DET	Detection test
DM	Diabetes mellitus
DMC	Data monitoring committee
[redacted]	[redacted]

[redacted]

Echo	Echocardiography
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ENR	Enrolled set run-in phase
EOS	End of study
EOT	End of treatment
FAS	Full analysis set
FAQ	Functional activities questionnaire
FLAIR	Fluid attenuated inversion recovery
FSH	Follicle stimulating hormone
GCCS	Global cognitive composite score
GCP	Good Clinical Practice
[redacted]	
GMLT	Groton maze learning test
γGT	Gamma-glutamyl transferase
HF	Heart failure
HFpEF	Heart failure and preserved ejection fraction
HFrEF	Heart failure and reduced ejection fraction
HIV	Human immunodeficiency virus
HTN	Hypertension
IADL	Instrumental activities of daily living
IB	Investigator brochure
ICF	Informed consent form
ICH	International council for harmonisation
IDT	Identification test
IEC	Independent ethics committee
IN	Investigator notification
IRB	Institutional review board
IRT	Interactive response technology
ISLT-DR	Interactive shopping list test delayed recall
IVRS	Interactive voice response system
LFT	Liver function test
LRS	LCZ696 run-in set
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MAR	Missing at random
MBq	Megabecquerel
MCCB	MATRICS cognitive assessment battery
MCHC	Mean corpuscular hemoglobin concentration

[redacted]

MCI	Mild cognitive impairment
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MID	Minimally important difference
MMSE	Mini mental state examination
MNAR	Missing not at random
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
NEP(i)	Neutral endopeptidase inhibitor
NSAIDS	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
ONB	One back test
PCI	Percutaneous coronary intervention
PDE-5	Phosphodiesterase inhibitor 5
PET	Positron emission tomography
PPS	Per protocol set
PT	Prothrombin time
QM	Quality management
RAN	Randomized set
RAS	Renin angiotensin system
RBC	Red blood cell
RDW	Red blood cell distribution width
SAE	Serious adverse event
SAF	Safety set
SBP	Systolic blood pressure
SCR	Screened set
SCr	Serum Creatinine
SD	Standard deviation
SIB	Suicidal ideation and behavior
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMQ	Standard medical query
SNRI	Serotonin norepinephrine reuptake inhibitor
SOP	Standard operating procedure
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reaction
SUVr	Standardized uptake value ratio

TBL	Total bilirubin
TD	Study Treatment Discontinuation
TSH	Thyroid stimulating hormone
ULN	Upper limit normal
US CFR	United States code of federal regulations
VRS	Valsartan run-in set
WBC	White blood cell
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 2

Amendment rationale

The purpose of this administrative amendment is to correct the typographical error in the clean version of the protocol amendment 1 with respect to the numbering of the exclusion criteria's that was starting at '2' instead of '1' (in the Section 4.2 Exclusion criteria). As of 18-Aug-2017 fifteen patients are randomized into the study.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the trial specific model ICF.

Amendment 1

The first amendment of protocol CLCZ696B2320 was dated 01-Jun-2017.

Amendment rationale

Recruitment in Study CLCZ696B2320, also known as PERSPECTIVE study, began on 26-Nov-2016. As of 1-Jun-2017 one patient is randomized into the study. Although CLCZ696B2320 study was designed as an independent study to evaluate cognitive function and cerebral amyloid accretion in HFpEF patients, most of the inclusion and exclusion criteria were derived from the PARAGON-HF trial (an event-driven trial) where they were thought not to impact the objectives of the CLCZ696B2320 study.

However experience to date suggests that the observed screen failure rate in CLCZ696B2320 study is considerably higher than originally anticipated. Many of the failures are due to patients not being able to meet the magnetic resonance imaging (MRI) cerebrovascular criteria. The existing MRI criteria were intended to exclude patients with significant cerebrovascular pathology in whom the rate of change in cognitive function over time may be different to those without significant background vascular disease. However, based on PERSPECTIVE study screening experience as well as available literature, the prevalence of cerebrovascular disease appears to be significantly higher than originally anticipated and the existing exclusion criteria appear to limit the population to the extent that the study cohort might not be truly reflective of the heart failure patients seen in the community. Therefore, in the interest of keeping the study population reflective of the HF population seen in the community, the amended protocol will no longer exclude cerebrovascular disease as assessed on the MRI criteria. Cerebrovascular disease burden will continue to be assessed as per the existing criteria, and the baseline value will be used as an additional independent variable in the statistical analysis modeling for the primary and relevant secondary endpoints. Patients

[redacted]

with clinically significant cerebral pathology, for example large cerebral aneurysm, space occupying lesion etc. will continued to be excluded from the study. In addition, some of the existing criteria taken from PARAGON-HF were originally developed to help identify patients at high risk for cardiovascular events which are not relevant for the objectives of CLCZ696B2320 study. Therefore this amendment aims to revise some of the study inclusion and exclusion criteria to remove unnecessary restrictions and to ensure the study population reflects the HFpEF population in the community. In addition, this amendment also corrects inconsistencies between various sections of the protocol, corrects typographical errors, and provides clarifications where instructions are less clear. Some of the key changes to the protocol are listed below.

None of the changes are expected to have major impact on the objectives or the analysis of the study results.

Changes to the protocol

Key updates to Section 4.1 (Inclusion criteria) and Section 4.2 (Exclusion criteria):

- NT-proBNP requirement is adjusted to ≥ 125 pg/mL to be consistent with new European Society of Cardiology guidelines.
- Prior heart failure hospitalization is removed as an eligibility criterion for inclusion in the study as this criterion by itself may not support a diagnosis of heart failure in the absence of NT-ProBNP values of ≥ 125 pg/mL.
- Removed the requirement to meet MRI criteria for cerebrovascular and white matter lesion. Clinically significant cerebral pathology that may impact cognition will remain as an exclusion criterion.
- Removed the existing exclusion criterion in order to allow participation of patients with a history of cardiomyopathies that have an ejection fraction of >40%; as exclusion of these patients is not relevant to the study objectives and these patients may benefit from treatment with LCZ696.
- Significant obstructive valvular disease is added as an exclusionary criterion as these patients are less tolerant to vasodilators.
- Listed the exclusions and restrictions regarding the use of sedative hypnotics, selective serotonin re-uptake inhibitors, serotonin norepinephrine re-uptake inhibitors which are described elsewhere in the protocol but are missing from Section 4.1.
- Clarification provided regarding the exclusionary criterion for thyroid function tests, Vitamin B12 or folate deficiency.

Updated Sections 5.3 and 6.5.1 to indicate that amyloid status results will not be made available to investigators.

Updated Section 5.5.4 by adding time window for dose administration instead of just starting time.

Assessment scheduled (Table 6-1) was updated to clarify that the plasma beta amyloid will be assessed only in patients participating in PET substudy.

Updated Section 6.5.1 to indicate that, the end of study (EOS) imaging procedures will be performed only when prior assessments were made more than 12 months ago.

[redacted]

Updated Sections 6.5.8.6 and 6.5.9 to clarify that FSH levels will be measured to confirm menopausal status in patients who have undergone oophorectomy without hysterectomy.

In Section 9.4, the cerebrovascular disease burden as measured by MRI was added as one of the independent variables in the statistical analysis modeling for the primary endpoint and relevant secondary endpoints. In Section 9.4.1 minor edit and additional clarification are added for the calculation of each composite score for GCCS battery to make the calculations more clear.

Additional minor changes were made to correct typographical errors and inconsistencies in the protocol.

[redacted]

Protocol summary

Protocol number	CLCZ696B2320
Title	A multicenter, randomized, double-blind, active-controlled study to evaluate the effects of LCZ696 compared to valsartan on cognitive function in patients with chronic heart failure and preserved ejection fraction
Brief title	Study to evaluate the effects of LCZ696 on cognitive function in patients with chronic heart failure (HF) and preserved ejection fraction (pEF)
Sponsor and Clinical Phase	Novartis, Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the effect of LCZ696 compared to valsartan on cognitive function in patients with HFpEF.
Primary Objective	To evaluate the effects of LCZ696 compared to valsartan on cognitive function over 3 years in patients with HFpEF as assessed by the CogState cognitive assessment battery.
Secondary Objectives	• To evaluate the effect of LCZ696 compared to valsartan on β-amyloid deposition in the brain in a subset of patients using amyloid positron emission tomography (PET) imaging over 3 years. • To evaluate the effects of LCZ696 compared to valsartan on individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the CogState battery over 3 years • To compare LCZ696 to valsartan in evaluating changes in instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) over 3 years.
Study design	This study is a multi-center, randomized, double-blind, parallel group, active comparator trial designed to evaluate the overall effect of LCZ696 compared to valsartan on cognitive function as assessed by the CogState comprehensive cognitive battery in patients with HFpEF.
Population	The study population will consist of 520 patients ≥ 60 years of age with chronic symptomatic HF (New York Heart Association (NYHA) class II-IV) and left ventricular ejection fraction (LVEF) > 40%.
Inclusion criteria	1. Written informed consent including consent for APOE4 gene testing must be obtained before any assessment is performed 2. Male or female patients aged ≥ 60 years of age. 3. Chronic heart failure with current symptom(s) (NYHA class II-IV) at Screening visit. 4. LVEF > 40% a. By any method using most recent assessment within 6 months prior to screening visit OR b. By an echocardiogram performed during the screening visit, if previous assessment is not available. 5. NT-proBNP ≥ 125 pg/mL at Screening visit

[redacted]

	6. Patient with evidence of adequate functioning (e.g.: intellectual, motor, visual and auditory) to complete the study assessments and has elementary education or 6 years of sustained employment.
Key Exclusion criteria	1. Current acute decompensated HF requiring augmented therapy with diuretics, vasodilators and/or inotropic drugs. 2. Acute coronary syndrome (including myocardial infarction (MI)), cardiac surgery, other major cardiovascular (CV) surgery, or urgent percutaneous coronary intervention (PCI), carotid surgery or carotid angioplasty, history of stroke or transient ischemic attack within the 3 months prior to Screening visit or an elective PCI within 30 days prior to Screening visit. 3. Patients with a history of hereditary or idiopathic angioedema or angioedema related to previous angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapies. 4. Patients who require treatment with 2 or more of the following: an ACEi, an ARB or a renin inhibitor. 5. Patients with one of the following: a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) formula at screening visit, **or** b. eGFR <25 mL/min/1.73m^2 at Visit 103 or at end of run-in / randomization visit, **or** c. eGFR reduction >35% (compared to Visit 1) at Visit 103 or Visit 199/201 6. MMSE score <24 at Screening visit 7. Patients with a clinical diagnosis of Alzheimer's disease or other dementia syndromes or any indication for or current treatment with cholinesterase inhibitors and/or another prescription Alzheimer's Disease (AD) treatment (e.g., memantine). 8. Any history of medical or neurological condition likely to affect the participant's cognition (e.g., clinically significant brain trauma with loss of consciousness > 3 minutes within 6 months prior to screening, Huntington's disease, Parkinson's disease, Lyme's disease, syphilis, HIV dementia, uncontrolled seizure disorder) or clinically significant abnormalities in thyroid function tests, Vitamin B12 or folate deficiency requiring treatment at screening (Patients who are adequately treated may be included at investigator discretion). 9. Inability to perform cognitive battery or other study evaluations based on significant motor (e.g. hemiplegia, muscular-skeletal injury) or sensory (blindness, decreased or uncorrected visual or auditory acuity) skill. 10. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the Columbia suicidality severity rating scale (C-SSRS), if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" question, if this behavior occurred in the past 2 years. 11. Clinically significant cerebral pathology, for example large cerebral aneurysm, space occupying lesion etc. that may impact cognition as assessed by MRI central reader. 12. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes. 13. History or presence of any other disease with a life expectancy of <3

[redacted]

	years 14. Women of child bearing potential defined as all women physiologically capable of becoming pregnant.
Investigational and reference therapy	LCZ696 50 mg (dose level 1), 100 mg (dose level 2), 200 mg (dose level 3) Valsartan 40 mg (dose level 1), 80 mg (dose level 2), 160 mg (dose level 3)
Efficacy assessments	Global cognitive composite score (GCCS) Cognitive domains of attention, memory, and executive function [redacted] Functional activities questionnaire (FAQ)
Safety assessments	[redacted] Physical examinations [redacted] Brain amyloid PET imaging [redacted] Plasma β-amyloid
Other assessments	[redacted] NT-proBNP
Data analysis	The primary endpoint, the change from Baseline to 3 years in the CogState Global Cognitive Composite Score (GCCS), will be analyzed using a repeated measures analysis of covariance (ANCOVA) model in which treatment, age stratification factor, MMSE stratification factor, region, education level, apolipoprotein E ε4 allele (APOE4) status (carrier vs. non-carrier), baseline cerebrovascular disease burden as measured by MRI (calculated based on four factors: lacunar infarcts > 2; cortical or subcortical infarct > 1cm^3; white matter lesion Fazekas score of 3; micro hemorrhages ≥4), visit (Weeks 26, 52, 78, 104, 130, and week 156) and treatment-by-visit interaction are included as fixed-effect factors and baseline GCCS and visit by baseline GCCS interaction as covariates, with a common unstructured covariance matrix among visits between treatment group. The adjusted mean changes at 3 years within each treatment group and standardized treatment group difference (Cohen's d) in mean change from baseline at 3 years will be presented with corresponding 95% confidence interval (CI) based on the above model. The primary analysis will be based on Safety set (SAF) including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment. The secondary efficacy variables are: 1. Change from baseline in individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the cognitive assessment battery at 3 years. 2. Change from baseline in the summary score of the instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) at 3 years. These secondary efficacy variables will be analyzed in a similar manner as the primary endpoint (GCCS). Safety endpoints to be analyzed are: 1. Change from baseline in a cortical composite SUVr (standardized

[redacted]

	uptake value ratio) at 3 years [redacted] Safety endpoint of change from baseline in a cortical composite SUVr (standardized uptake value ratio) at 3 years will be based on a model based multiple imputation approach under missing at random (MAR) assumption. The imputation model will be fitted separately within each treatment by baseline amyloid status (positive/ negative) group with intercept, age stratification factor, MMSE stratification factor, region, baseline cerebrovascular disease burden as measured by MRI, ApoE4 status (carrier vs non-carrier) and time (when the SUVr is assessed in days) as fixed effects including a subject-specific random intercept and slope (time) and a common unstructured covariance. Treatment effect on change from baseline to 3 years in SUVr as estimated from each imputed dataset following an ANCOVA model using treatment, age stratification factor, MMSE stratification factor, region, ApoE4 status, baseline amyloid status as factors and baseline SUVr value as covariate, will be combined using Rubin's rule to provide overall inference. The adjusted mean change at 3 years within each treatment, the difference in mean change at 3 years between two treatments and, its 95% confidence interval will be presented. The analysis will be based on safety set using 'on-treatment' data. Other safety variables, unless otherwise mentioned, will be descriptively and graphically summarized at each assessment visit separately for run-in and double blind period. It is estimated that approximately 180 patients per group would provide • at least 80% probability that the 2-sided 95% CI excludes a standardized effect size (Cohen's d) of 0.3 (or greater) in change in composite z-score of the battery test over 3 years, given that there is no expected difference between the two treatments. • at least 80% probability that the 2-sided CI excludes 0 (corresponding to $p < 0.05$), if the true standardized effect size is 0.3 or greater (in either direction) Approximately 300 patients (in 1:1 allocation ratio to LCZ696 and valsartan) will provide at least 80% probability that the 2-sided 95% CI excludes a between-treatment absolute difference of 0.01 (corresponding to an incremental 33% increase in LCZ696 vs. valsartan) in change from baseline in SUVr over 3 years if there is no expected difference between the two treatments. To account for potential loss in information due to estimated 30% drop out rate, approximately 520 patients are planned to be randomized.
Key words	heart failure and preserved ejection fraction, cognitive function, brain amyloid PET imaging, [redacted] Global cognitive composite score, APOE4, functional activities questionnaire, [redacted] plasma beta amyloid

[redacted]

1 Introduction

1.1 Background

Heart failure (HF) is a major public health problem associated with a high mortality rate, frequent hospitalizations, and poor quality of life. Despite existing treatment options, heart failure remains a progressive syndrome with a high mortality rate, and an illness with an unmet need for new therapies to improve health outcomes (McMurray et al 2012).

LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI) for the treatment of patients with chronic heart failure and reduced ejection fraction (HFrEF). After ingestion, LCZ696 delivers systemic exposure to sacubitril (AHU377), a neprilysin inhibitor pro-drug, and valsartan, an angiotensin receptor blocker (ARB). Neprilysin (neutral endopeptidase, (NEP)) is a naturally occurring membrane-bound enzyme, responsible for the degradation of natriuretic peptides and other peptide hormones such as adrenomedullin, bradykinin, substance P, angiotensin I and II, β-amyloid, and possibly endothelin-1. LCZ696, through its unique mode of action potentiates beneficial endogenous vasoactive peptides via NEP inhibition while inhibiting the Renin Angiotensin System (RAS) via angiotensin II type 1 receptor blockade; both mechanisms are considered to act in a complementary and additive manner to improve outcome in patients with HFrEF.

Consistent with this mechanism of action, the recently completed landmark randomized trial (PARADIGM-HF, N=8442) demonstrated that LCZ696 was superior to enalapril (current standard of care) in reducing cardiovascular (CV) death and heart failure hospitalization in patients with HFrEF. The magnitude of these advantages of LCZ696 over an angiotensin converting enzyme (ACE) inhibitor was statistically significant and clinically relevant, particularly since the drug was compared with current standard of care with an established mortality benefit in HF patients (McMurray et al 2014). In this study, compared with enalapril (ACEi), LCZ696 demonstrated a 20% risk reduction for HF hospitalization or CV death (primary endpoint, p = 0.0000002), 20% risk reduction in CV death alone (p=0.00004), and 21% risk reduction for first HF hospitalization (p=0.00004). In addition, LCZ696 also demonstrated benefit in symptom improvement, total HF hospitalization, all cause hospitalization and emergency room visits compared to enalapril. LCZ696 is currently under investigation for patients with heart failure and preserved ejection fraction (HFpEF) in an ongoing large randomized clinical trial (PARAGON-HF, 4600 patients with HFpEF), where no standard of care is available.

Cognitive impairment has been reported in patients with heart failure in several studies over the past three decades. The prevalence of cognitive impairment observed in these heart failure studies (no distinction made between HFrEF or HFpEF) ranged from 25 to 75% (Ampadu and Morley 2015, Cannon et al 2015). Changes in cognition as a result of improved cardiac function have not been extensively evaluated. However, studies in heart failure patients implanted with a left ventricular assist device showed that cognition, as assessed by a comprehensive battery of tests, was improved during follow-up ranging from 6 months to 2 years (Simoni et al 2014).

[redacted]

Observational epidemiological studies have shown a relationship between cognitive impairment and elevated blood pressure (BP). For example, the Honolulu-Asia Aging Study revealed that systolic blood pressure in midlife was associated with cognitive impairment later in life (Launer et al 2000). In another longitudinal study that followed elderly patients in Sweden, an association was shown between blood pressure at age 70 and the subsequent development of dementia 10 to 15 years later (Skoog et al 1996). Thus, a reasonable expectation would be that antihypertensive therapy should slow cognitive decline. However, the effect of blood pressure lowering on cognition, although extensively studied, has yielded inconsistent findings. These conflicting results are likely due to the use of different study designs, varying baseline blood pressures, inconsistent inclusion criteria, and most importantly, inadequate power to detect meaningful responses (Gorelick and Nyenhuis 2012). Nevertheless, it is therefore possible that an improvement in cardiac function and blood pressure per se, as a result of long-term drug treatment, with LCZ696, may result in beneficial effects on cognition.

Cognitive decline is also observed in patients with a history of stroke or vascular disease detected by neuroimaging. Cognitive impairment associated with cerebrovascular dysfunction is classified as "vascular cognitive impairment" (Gorelick et al 2011). In contrast, cognitive functional changes that are evident in Alzheimer's Disease (AD) are associated with beta amyloid (Aβ) neuritic plaques and neurofibrillary tangles. These two conditions (deposition of neuritic plaque and changes in cerebrovascular structure and function) can exist concurrently in elderly patients and is now being described as one entity, known as "mixed dementia". Moreover, there is likely a complex interplay between the pathological processes leading to these various dementias.

Alzheimer's disease is a complex, multifactorial disease that develops over a long period of time (15-20 years), and is associated with the presence of amyloid beta (Aβ) plaques in the brain. The Aβ42 isoform is primarily found in amyloid plaques, whereas the Aβ40 isoform is primarily found in amyloid angiopathy (Mawuenyega et al 2010). In addition to degrading the biologically active vasoactive peptides mentioned above, *in vitro* and non-clinical studies have shown that neprilysin is one of multiple enzymes involved in the proteolytic degradation of Aβ. Other proteases with Aβ-degrading properties include insulin-degrading enzyme, endothelin-converting enzyme, ACE, and plasmin (Wang et al 2006). Besides enzymatic degradation of Aβ, it is also removed from the brain by other processes including transport into cerebrospinal fluid (CSF) and the bloodstream (Saido and Leissring 2012). The relative importance of each of these pathways for proteolytic degradation of Aβ in humans is unknown, but neprilysin inhibition could potentially reduce the clearance of Aβ from the central nervous system (CNS). Reduced clearance of Aβ from the brain over a prolonged period of time could theoretically result in an accumulation of Aβ in brain parenchymal plaque, which may increase the risk of development of AD.

To gain a better understanding of the impact of neprilysin inhibition on Aβ metabolism, a 2-week study in young cynomolgus monkeys (2-4 year old) was undertaken, and Aβ concentrations in CSF and brain tissue were assessed during treatment with LCZ696. The dosing regimen (50 mg/kg/day) in the monkey resulted in a systemic drug exposure similar to LCZ696 400 mg once daily dosing in man. In this study, LCZ696 treatment resulted in an acute decrease in clearance of CSF Aβ42 on Day 1, and increase in total CSF Aβ42 and Aβ38

[redacted]

on Day 15. It is important to note that by Day 15 clearance of Aβ42 was no longer significantly decreased relative to controls, and brain tissue concentrations of Aβ were not affected by LCZ696 compared to vehicle. The human translatability and potential consequences of these changes in CSF Aβ clearance are currently not known.

In contrast to the sub-acute cynomolgus monkey study where increases in CSF Aβ42, Aβ40 and Aβ38 concentrations in CSF were observed, oral administration of LCZ696 400 mg once daily in healthy subjects for 14 days did not result in changes in Aβ42 and Aβ40 in the CSF. However, there was an increase in CSF Aβ38 in these healthy subjects. The clinical relevance of this increase in CSF Aβ38 in this study is unknown, as there is no evidence that an isolated increase in Aβ38 concentration facilitates Aβ plaque formation. These observations suggest that enzymes and disposition pathways other than neprilysin may be important in clearance of CSF Aβ in humans.

In a chronic toxicology study in cynomolgus monkeys treated with LCZ696 at 300 mg/kg/day for 39-weeks, there were no increases in brain immunostaining for Aβ42, plaque formation, or compound-related microscopic brain changes. This 300 mg/kg/day dose in monkeys resulted in an approximately 10-fold greater maximum concentration (Cmax) in plasma than a 400 mg once daily dose in humans.

Furthermore, in PARADIGM-HF where patients with HFrEF have been treated with LCZ696 for up to 4.3 years, there was no increased incidence of AD or dementia-related adverse events compared to patients treated with current standard of care. The age of patients in PARADIGM-HF was 63.8 ± 11.5 (mean ± SD). Similarly, in the 36 week PARAMOUNT study in patients (70.9 ± 9.4 years of age) with HFpEF, there was no increased incidence of AD or dementia-related adverse events in LCZ696-treated patients compared to patients receiving valsartan. However, these studies were not prospectively designed to specifically evaluate the effect of LCZ696 on AD or dementia.

The overall net effect of these various factors on cognition has not been specifically studied. For example, the potential long-term effects on the clearance of Aβ as a result of neprilysin inhibition via LCZ696 and potential cognitive benefit derived from improved cardiac and hemodynamic function as a result of chronic LCZ696 treatment remain unknown. The primary goal of the current study is to assess the overall impact of long-term LCZ696 therapy compared to valsartan on cognitive function assessed via a comprehensive battery of neuropsychological tests in patients with HFpEF. In addition, β-amyloid deposition in brain will be assessed using positron emission tomography amyloid (PET) imaging.

1.2 Purpose

The purpose of this study is to evaluate the effect of LCZ696 compared to valsartan on cognitive function in patients with HFpEF. Cognitive function will be assessed using the CogState comprehensive battery of tests, which include a longitudinal evaluation of key cognitive domains such as memory, executive function, and attention.

In addition, the effect of LCZ696 therapy compared to valsartan on amyloid plaque deposition in the brain will be evaluated in a subset of patients using amyloid florbetapir ^{18}F PET imaging.

[redacted]

2 Study objectives and endpoints

2.1 Primary objective(s)

To evaluate the effects of LCZ696 compared to valsartan on cognitive function over 3 years in patients with HFpEF as assessed by the CogState cognitive assessment battery.

2.2 Secondary objective(s)

- To evaluate the effect of LCZ696 compared to valsartan on β-amyloid deposition in the brain in a subset of patients using positron emission tomography amyloid (PET) imaging over 3 years.
- To evaluate the effects of LCZ696 compared to valsartan on individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the CogState battery over 3 years
- To compare LCZ696 to valsartan in evaluating changes in instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) over 3 years.

2.3 Exploratory objectives

[redacted]

2.4 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate the effects of LCZ696 compared to valsartan on cognitive function over 3 years in patients with HFpEF as assessed by the CogState cognitive assessment battery.	Change from baseline to 3 years in the CogState Global Cognitive Composite Score (GCCS)	Section 9.4.1
Secondary		
To evaluate the effect of LCZ696 compared to valsartan on β-amyloid deposition in the brain in a subset of patients using amyloid positron emission tomography (PET)	Change from baseline in a cortical composite SUVr (standardized uptake value ratio) at 3 years	Section 9.5.2

[redacted]

Objective	Endpoint	Analysis
imaging over 3 years		
To evaluate the effects of LCZ696 compared to valsartan on individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the CogState battery over 3 years	Change from baseline in individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the cognitive assessment battery at 3 years	Section 9.5.1
To compare LCZ696 to valsartan in evaluating changes in instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) over 3 years	Change from baseline in the summary score of the instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) at 3 years	Section 9.5.1
Exploratory		
[redacted]	[redacted]	[redacted]

[redacted]

Objective	Endpoint	Analysis
[redacted]		

3 Investigational plan

3.1 Study design

This study is a multi-center, randomized, double-blind, parallel group, active comparator trial designed to evaluate the overall effect of LCZ696 compared to valsartan on cognitive function as assessed by a comprehensive cognitive battery in patients with HFpEF (Figure 3-1). The study population will consist of patients ≥60 years of age with chronic symptomatic HF (NYHA class II-IV) and a left ventricular ejection fraction (LVEF) >40%. Patients will be randomized in a 1:1 fashion to either LCZ696 200 mg bid or valsartan 160 mg bid.

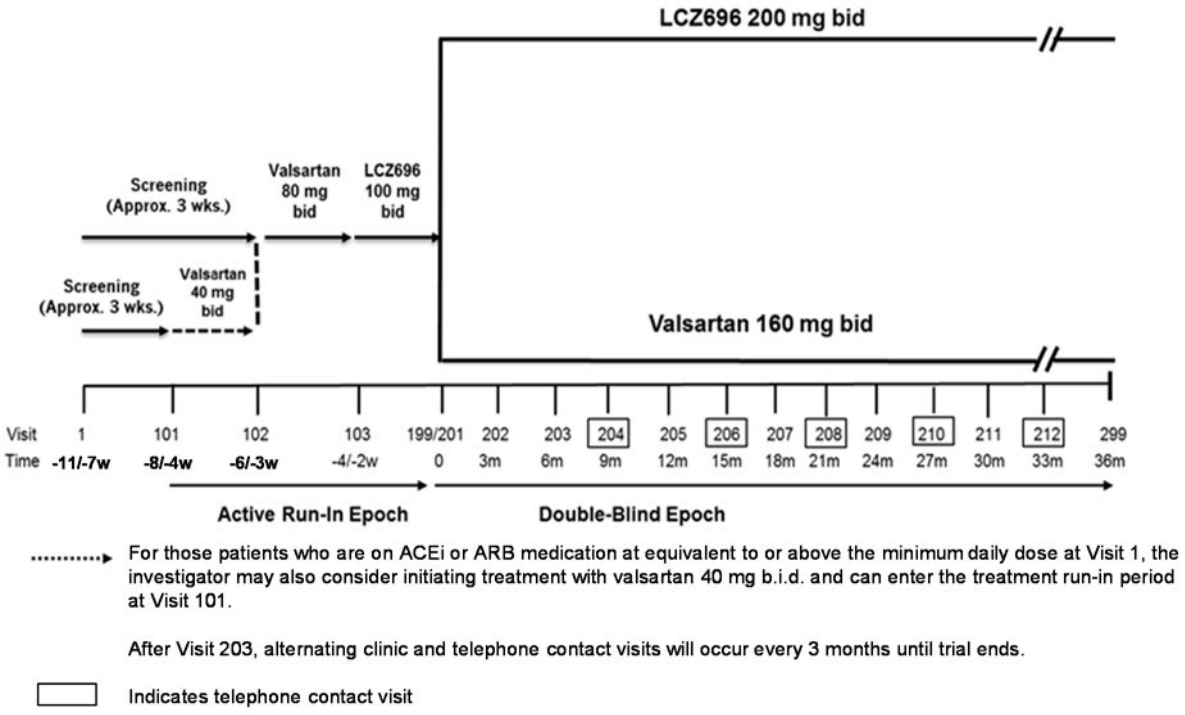
Cognitive function will be assessed at baseline and every six months up to 3 years by a comprehensive cognitive battery, and MMSE will be assessed annually. Patients scoring <24 on the MMSE scale during screening will be excluded from the study. Patients will be stratified based on age (< 75, ≥ 75 years), MMSE score (< 28, ≥ 28), and if participating in the PET imaging substudy, amyloid status (amyloid positive/negative). APOE4 is a strong predictor of cognitive impairment (Lim et al 2015) and Aβ accumulation. Therefore, patients will be genotyped for APOE4 allele status.

The study will also evaluate the impact of LCZ696 therapy compared to valsartan on β-amyloid deposition in the brain using florbetapir ^{18}F PET imaging in a subset of patients. PET imaging requires specialist centers experienced in the technique that are in close proximity to a radiopharmaceutical production facility, thus a subset of centers will be selected as PET centers. To ensure high quality of imaging data, PET imaging will be conducted in all eligible patients at selected PET capable centers. Amyloid PET imaging will be performed at randomization, at 18 months, and at 3 years (EOS Visit). If a patient permanently discontinues treatment prior to 3 years, a PET scan should be done at the end of treatment visit (EOT visit) if a prior scan was performed more than twelve months ago. End of study (EOS) scan will not be required if EOT scan is performed within 12 months of end of study visit. All PET scans will be evaluated centrally.

Brain magnetic resonance imaging (MRI) will be performed at the Screening visit in all patients to evaluate exclusion criteria, at 18 months, at the end of treatment visit (EOT Visit, only if prior scans were performed more than twelve months previously), and at the end of study visit. With the exception of the screening MRI, subsequent MRI scans will only be performed in the sub-set of study patients for which PET is being performed. All MRI scans will be evaluated centrally. Baseline MRI scans at screening will assist in determining patient eligibility for the study. Magnetic resonance images will also be used to assess global and regional brain structural volume at baseline and at end of study.

[redacted]

Figure 3-1 Study design



bid – twice daily dosing

Screening epoch

A Screening epoch of approximately 3 weeks will be used to assess eligibility.

To minimize unnecessary patient assessment burden, sites are strongly advised to administer Cognitive assessments (MMSE, [redacted] FAQ, [redacted] CCB) only after confirming that the screening laboratory data are available and the patient is considered otherwise eligible to participate in the study. Cognitive assessments should ideally be administered by the same assessor in a quiet environment and prior to any other clinical assessments scheduled during the day. The investigator must ensure patient eligibility on all inclusion/exclusion criteria including laboratory and MMSE assessments prior to performing the MRI scan. It takes up to five days to confirm eligibility from the central MRI reader. The sites should take this into consideration when scheduling MRI scans.

A patient who enters screening but is determined not to be eligible to enter the treatment run-in period will be considered a screen failure. The investigator may consider re-screening the patient at a later time if he/she believes that the patient's condition has changed and may potentially be eligible. A minimum of 2 weeks must elapse between re-screenings and a patient may be re-screened once only. Patients who have screen failed based on MRI criteria for cerebral and vascular pathology in the original protocol may be eligible to be rescreened after implementation of protocol amendment 1. In those patients if previous study MRI scan was performed within 6 months of re-screening date this will be considered baseline assessment for these patients and no further baseline scans will be acquired.

[redacted]

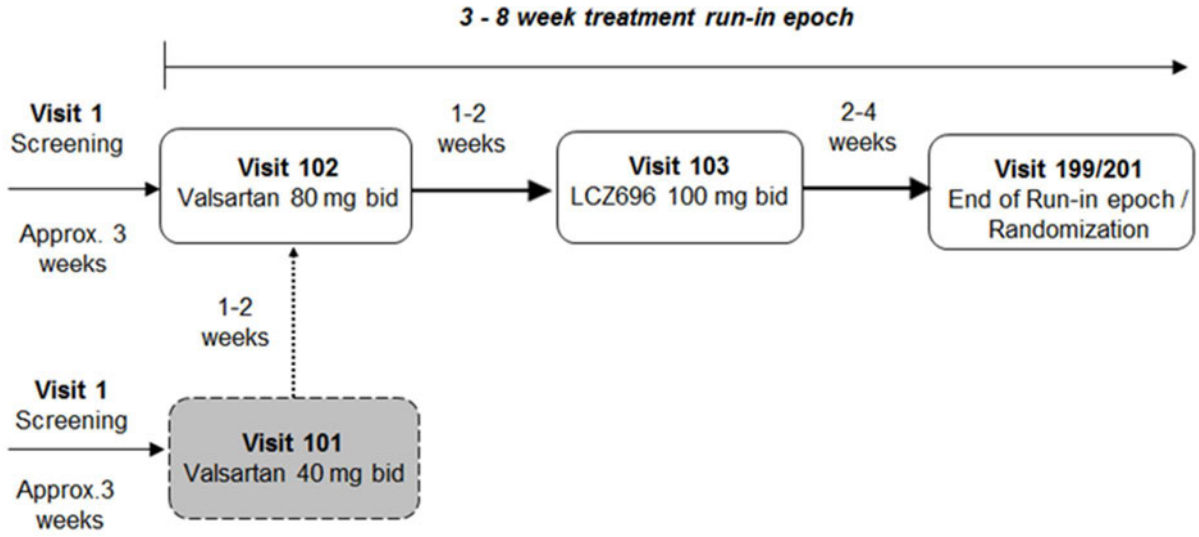
Single-blind treatment run-in epoch

The single-blind treatment run-in period is designed to assess patient's tolerability to study drug, and to determine patients who are likely to stay on study drug for the duration of the trial.

The treatment run-in period consists of valsartan 40 mg bid (if necessary), followed by valsartan 80 mg bid and then followed by LCZ696 100 mg bid, over 3 to 8 weeks duration (Figure 3-2). During the run-in period, patients will continue their background HF medications with exception of ACEi, ARB or renin inhibitor which will be discontinued. The concomitant use of ACEi, ARB or renin inhibitor during the treatment run-in is strictly prohibited. Patients will enter the treatment run-in period based on their use of RAS blockade medications at the time of screening (Figure 3-2 and Table 3-1). Patients unable to tolerate either valsartan or LCZ696 during the run-in will not be eligible for randomization, and will be discontinued from the study. This design will allow a careful assessment of the patient's tolerability to study medications prior to randomization.

Patients will enter different parts of the treatment run-in period based on their use of RAS blockade medications at the time of enrollment. Patients should enter the treatment run-in period at Visit 102 starting valsartan 80 mg bid if they have been on an ACEi or ARB medication at a dose which is equivalent to or above the total daily doses listed in Table 3-1. Otherwise, patients should enter the treatment run-in epoch at Visit 101 starting with valsartan 40 mg bid for 1 to 2 weeks before they start valsartan 80 mg bid at Visit 102. However, at the investigator's discretion, those patients who are on ACEi or ARB medication at equivalent to or above the total daily dose listed in Table 3-1 can also enter the treatment run-in epoch at Visit 101 starting valsartan 40 mg bid.

Figure 3-2 Treatment run-in epoch overview



bid – twice daily dosing

[redacted]

Table 3-1 Minimum pre-study total daily doses of commonly used ACEis and ARBs allowing patients to begin the treatment run-in epoch at Visit 102 (valsartan 80 mg bid)

ACEI	Dose	ARB	Dose
Benazepril	20 mg	Azilsartan	40 mg
Captopril	100 mg	Candesartan	16 mg
Cilazapril	2.5 mg	Eprosartan	400 mg
Enalapril	10 mg	Irbesartan	150 mg
Fosinopril	20 mg	Losartan	50 mg
Imidapril	10 mg	Olmesartan	10 mg
Lisinopril	10 mg	Telmisartan	40 mg
Moxepril	7.5 mg	Valsartan	160 mg
Perindopril	4 mg		
Quinapril	20 mg		
Ramipril	5 mg		
Trandolapril	2 mg		
Zofenopril	30 mg		

Patients who meet the safety monitoring criteria (Table 3-2) at Visit 103 will proceed to treatment with LCZ696 100 mg bid for 2 to 4 weeks.

Study drug should not be dispensed unless the patient meets all inclusion criteria and none of the exclusion criteria at Visit 1 and subsequently at Visit 199/201.

Table 3-2 Safety monitoring criteria that must be met at Visit 1 (screening), Visit 103 and Visit 199/201

Parameter	Visit 1 (Screening)	Visits 103 (treatment run-in) and Visit 199/201 (end of treatment run-in/randomization)
Potassium level	K ≤5.2 mmol/L (mEq/L)	K ≤5.4 mmol/L (mEq/L)
Kidney function	eGFR ≥30 mL/min/1.73m^2	eGFR ≥25 mL/min/1.73m^2 eGFR reduction <35% compared to Visit 1
Blood pressure	SBP ≥110 mmHg	No symptomatic hypotension as determined by the investigator and SBP ≥100 mmHg.
AEs or conditions	No conditions that preclude continuation according to the investigator's judgment	No postural symptoms or any AEs that preclude continuation according to the investigator's judgment

AE – adverse event

To assess the patient's eligibility to continue in the study, either local or central laboratory should be used for the assessment of potassium and estimated glomerular filtration rate (eGFR) at Visits 103 and 199/201 (end of treatment run-in visit/randomization). If central laboratory is used, since it may take up to 72 hours to obtain the results, it is recommended that the site take this into consideration when scheduling subsequent study visits, while keeping the patient on the study medication. If a local laboratory is selected, the same samples should also be sent to the central laboratory, while the evaluation should be solely based on the local laboratory results. Patients should NOT enter Visits 103 or 199/201 without evaluating the safety monitoring criteria (Table 3-2).

[redacted]

Down-titration of study drug is not allowed during the treatment run-in period. Patients who are not able to tolerate study drug at the doses prescribed during the treatment run-in epoch will be discontinued.

Investigators may consider adjusting (dose reduced or discontinued) background medications (e.g., diuretic(s), antihypertensive agents, cardiovascular medications such as beta blockers, MRAs, nitrates, etc.) if the study drug is not tolerated (e.g., occurrence of AEs such as hyperkalemia, hypotension, and renal dysfunction) to ensure patients meet the safety criteria in Table 3-2 during the treatment run-in epoch. Patients may be seen at any time for unscheduled visits during the treatment run-in epoch for re-evaluation of safety criteria parameters.

Patients who experience angioedema at any time during the treatment run-in epoch must be discontinued from the study.

Patients who are discontinued from the treatment run-in epoch due to intolerance to the study drug, development of angioedema or for failure to meet the specified safety criteria will be considered treatment run-in failures and are not eligible to be re-screened for study entry.

At the end of the treatment run-in epoch (Visit 199/201), patients who meet the safety criteria (Table 3-2) and tolerate LCZ696 100 mg bid for at least 2 weeks are eligible for randomization. For these patients, Visit 199 and 201 occurs over a period of multiple days. Patients should be instructed not to take their morning (am) dose of treatment run-in study drug on the day they start randomized study drug.

Randomized treatment epoch

At randomization (Visit 199/201), eligible patients will be randomized to 1 of 2 treatment arms, either LCZ696 200 mg bid or valsartan 160 mg bid in a 1:1 fashion.

Every attempt should be made to maintain patients on the target study drug dose (dose level 3) (Table 3-3) throughout the trial. If the patient does not tolerate the target study drug dose level the investigator should consider, if appropriate, adjusting background medications to rectify the situation before considering down-titration to the next lower study drug dose level (Section 5.5.5).

Table 3-3 Study drug dose levels during randomized treatment epoch

Dose level	LCZ696 Treatment Arm	Valsartan Treatment Arm
3	200 mg bid	160 mg bid
2	100 mg bid	80 mg bid
1	50 mg bid	40 mg bid

At each dose level the patient will also take matching placebo for the other treatment arm study drug.

Study drug dose level adjustments should be based on overall safety and tolerability with special focus on a) hyperkalemia, b) symptomatic hypotension, and c) clinically significant decrease in eGFR/increase in serum creatinine (SCr). Treatment guidance for hyperkalemia, management of BP, and renal dysfunction are provided in Appendix 3, Appendix 4, and Appendix 5, respectively.

[redacted]

3.2 Rationale for study design

The key study design features of this study, including the run-in period, target dose, comparator and dose selection are largely similar to the current ongoing PARAGON-HF study (CLCZ696D2301) which is a Phase 3 outcome study comparing LCZ696 with valsartan in reducing CV death and HF hospitalization in patients with HFpEF. The data from this study are intended to be complementary to the data from the PARAGON-HF study.

Study Population:

The study population will consist of patients 60 years and older with chronic heart failure (NYHA class II-IV) and LVEF > 40%. LCZ696 has been shown to improve survival and reduce heart failure-related hospitalization in patients with HFrEF (LVEF ≤ 40%). Hence the study population consists of patients with HFpEF (LVEF >40%), as it is considered unethical to randomize HFrEF patients in this long term study to the valsartan treatment group. HFpEF is a condition that predominantly affects an elderly population. Age is also an important risk factor for cognitive decline and amyloid deposition. The entry requirement of 60 years or older and symptomatic heart failure will ensure that patients who are likely to benefit from LCZ696 therapy are included in the study while allowing the ability to study the potential effects on cognitive function in a relevant population. As treatment with LCZ696 has been demonstrated to confer significant mortality and morbidity benefit compared to current standard of care (ACEI) to patients with HFrEF, these patients will be excluded from the study. However, given the similarity of the population and patient characteristics, the results of this study should be relevant to the heart failure population at large regardless of ejection fraction.

The study aims to assess the effect of LCZ696 compared to valsartan on cognitive function in patients with normal cognition and mild cognitive impairment (MCI), while excluding patients with significant impairment, (e.g. patients with an MMSE score of <24; Holsinger et al 2007). Available data suggest that amyloid plaque deposition may reach a plateau once a patient is clinically diagnosed with AD (Bateman et al 2012). The rate of cognitive decline in AD patients is not uniform as it is dependent on various factors. Hence patients with a clinical diagnosis of AD or dementia will also be excluded from this study.

Further details about the patient population are provided in Section 4.

Active run-in period:

The single-blind epoch will help ensure that only patients who are likely to tolerate and maintain study drug for the long term follow-up are randomized; this will minimize the potential for early drop out, which is critical to assess the impact of long-term therapy of study medications for up to 3 years on cognitive function. In addition, the single blind treatment run-in epoch mimics clinical practice (where patients are only continued on treatments if they are tolerated).

The current treatment run-in design will assess the safety and tolerability of patients to drug dose level 2 (LCZ696 100 mg bid). Drug dose level 3 (LCZ696 200 mg bid) is not included in the run-in design as the great majority of patients who tolerated 100 bid were able to tolerate 200 bid in the run-in period of the PARADIGM-HF trial.

[redacted]

Baseline assessments will be made at the time of randomization visit following exposure to both study medications in the run-in period. In addition, brief exposure with LCZ696 during the run-in period is unlikely to have an impact on baseline study assessments.

Primary endpoint selection:

The primary endpoint of the study is change in cognition, which is assessed as the change in the Global Cognitive Composite Z scores (GCCS) from baseline (randomization) over 3 years.

There is no absolute or clear demarcation between cognitive domains affected in Alzheimer's dementia compared to vascular dementia. However some distinctions can be made between the two conditions in terms of the domains that are predominantly affected. For example, executive function is typically the primary cognitive impairment in vascular dementia. In contrast, cognitive domains encompassing memory functions are more often affected in Alzheimer's dementia although other faculties are also affected (Cavalieri et al 2010, Gorelick et al 2011, Lim et al 2012). Thus a composite score of relevant domains provides a comprehensive assessment of cognitive function in the study population.

The principle of using cognitive composite is well established and has been used in multiple studies in AD and depression (Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog), MATRICS cognitive assessment battery (MCCB); Raghavan et al 2013, Vellas et al 2015, Maruff and Jaeger 2015). The Alzheimer's Prevention Initiative has recommended the use of a composite clinical assessment as a primary endpoint rather than selecting a single cognitive assessment or individually examining multiple cognitive assessments (Langbaum et al 2015). A similar approach has been advocated by the Alzheimer's Disease Cooperative Study group (Donohue et al 2014).

The specific domains of cognition to be measured include psychomotor function, visual attention, working memory, executive function, visual learning and verbal learning and memory. These cognitive functions have been selected on the basis of their known sensitivity to changes in amyloid levels (Villemagne et al 2013, Lim et al 2014) and cerebral vascular function (Collie et al 2002, Clark and McDougall 2006, Steinberg et al 2015,) in humans. The cognitive functions will be measured using a set of computerized neuropsychological tests from the CogState Cognitive Battery (CCB) (Maruff et al 2013, Mielke et al 2014). The tests from the CCB have been selected on the basis of their extensive use and demonstrated sensitivity to cognitive decline associated with heart disease (Hammers et al 2013, Arslanian-Engoren et al 2014, Cannon et al 2015, Lansky et al 2015, Chou et al 2015), preclinical Alzheimer's disease (Darby et al 2011, Lim et al 2013, Lim et al 2015) and cerebrovascular disease (Silbert et al 2004, Steinberg et al 2015, Lansky et al 2015). Changes in performance on the CCB have also been shown repeatedly in response to treatment with central nervous system (CNS) active drugs (Thomas et al 2008, Padmanabhan et al 2009, Kay et al 2012, Grove et al 2014, Snyder et al 2014).

The CCB has been selected as it is designed specifically for repeated administration with minimal practice or learning effects and performance on the cognitive tests themselves are not influenced by the language, cultural or educational background of participants. Computer based testing allows the CCB to be administered in clinical trials by trained but non-expert clinical trials staff, which makes it ideal for use in a heart failure population (Lim et al 2014).

[redacted]

The three year duration was chosen for the study as available literature suggests that clinically relevant deterioration in cognition is associated with increases in amyloid deposition and is demonstrable over a period of 36 months (Villemagne et al 2011, Chen et al 2015). Although cognitive decline in the setting of AD occurs gradually, in several studies enrolling patients with mild cognitive impairment, patients progress to dementia at a rate of about 15% per year, with the majority of patients converting to frank dementia after 3 to 4 years (Belleville et al 2014).

Older adults who are cognitively normal but who show elevated levels of amyloid at their initial assessment have an increased rate of progression to clinically classified MCI or dementia over 36 months, when compared to those with low levels of amyloid. This rate of clinical disease stage progression is increased dramatically if individuals with high levels of amyloid also meet clinical criteria for MCI at their initial assessment. In addition, data from previous studies in heart failure suggest that more than a third of patients are no longer on study medication by 3 years (I-Preserve study; Massie et al 2008). Thus the 3 year duration is considered to provide an appropriate time period to study the trial objectives while retaining as many evaluable patients as possible.

Secondary endpoint selection:

Amyloid PET imaging

Change in brain amyloid deposition assessed by PET scanning is a key secondary endpoint. Two studies (Chen et al 2015, Landau et al 2015) have shown that longitudinal change in brain amyloid plaque load over 2 years can be demonstrated using amyloid PET imaging. The data from these studies indicates that changes in amyloid deposition may be greater among non-demented elderly individuals with worsening cognitive function compared to stable cognitive function during a 2 year interval. Similar observations were reported from other prospective studies which have shown that high cerebral Aβ load in non-demented subjects was associated with greater decline in episodic and working memory and is demonstrable by 18 months (Lim et al 2012). The current study enrolls non-demented patients regardless of their baseline amyloid status. Given that the expected rate of deposition of amyloid in this population is variable, this study will assess amyloid PET change and cognitive function over a 3 year period while the majority of patients are still likely to be continuing on study medication. The study will assess the change in a composite cortical florbetapir ^{18}F standardized uptake value ratio (SUVr) as a measure of amyloid plaque load.

Instrumental activities of daily living (IADL) as assessed by Functional Activity Questionnaire (FAQ)

Performance of activities of daily living is an important factor that significantly impacts a patient's quality of life. Intact activities of daily living (ADL) are often used as criteria to distinguish MCI from dementia. FAQ provides a standardized assessment of instrumental ADLs with high sensitivity to identify functional impairment. As functional changes in instrumental activities of daily living (IADL) that require higher cognitive ability are seen earlier in the dementia process, these will be evaluated using the Functional Activities Questionnaire (FAQ). This functional assessment of the patient using the FAQ will

[redacted]

complement the GCCS by providing an additional tool to monitor cognitive function, physical health, and functional capacity (Castilla-Rilo et al 2007).

[redacted]

3.3 Rationale for dose/regimen, route of administration and duration of treatment

LCZ696 dose of 200 mg twice daily was chosen as the target dose because it delivers similar valsartan exposure (assessed by area under the curve (AUC)) as Diovan® (valsartan) 160 mg twice daily and is the approved target dose for patients with heart failure. Furthermore, biomarker analysis and modeling indicate that the 200 mg dose of LCZ696 delivers approximately 90% of its maximal NEP inhibition. Twice daily dosing schedule is considered necessary for sustained NEP inhibition over a 24-hour period and it is anticipated to reduce the incidence of hypotension in HF patients, particularly in elderly patients. LCZ696 200 mg bid has been utilized in the recently completed Phase 3 PARADIGM-HF trial in HFrEF, and Phase 2 trial in HFpEF (PARAMOUNT), as well as the currently ongoing Phase 3 PARAGON-HF trial in HFpEF. The LCZ696 200 mg b.i.d dose was well tolerated and a significant majority of patients were maintained on this dose level in the completed studies.

[redacted]

Dosing is based on the total amount of both components of LCZ696, that is, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg as sacubitril/valsartan sodium salt complex and is referred to as LCZ696 50 mg, 100 mg, and 200 mg respectively.

3.4 Rationale for choice of comparator

There is no proven therapy to date that has convincingly been shown to reduce morbidity and mortality in patients with HFpEF (Yusuf et al 2003, Cleland et al 2006, Massie et al 2008). Valsartan is being given to treat the comorbidities that are prevalent in HFpEF, such as hypertension (HTN), diabetes mellitus (DM), and coronary artery disease where there is an indication for RAS blocking therapy (McMurray et al 2012). Data from studies in patients with HFpEF suggest that background ACEi or ARBs for treating comorbidities is common practice, including the recent TOPCAT study where a RAS blocker was used in 85% of patients at baseline (Desai et al 2011). Valsartan was chosen as the RAS blocker comparator because it is one of the commonly prescribed ARBs, and the target dose of LCZ696 200 mg delivers systemic exposure similar to the target dose of valsartan 160 mg. Patients in both groups will receive a similar amount of valsartan, which will allow careful assessment of neprilysin inhibition on cognitive function and the sign/symptoms of HF. In the PARAGON-HF study valsartan is also used as the comparator. Furthermore, a placebo comparator is not considered appropriate in this long term trial, as the comorbidities commonly present in HFpEF patients typically require RAS inhibition (i.e., ACEi or ARB).

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable

3.6 Risks and benefits

LCZ696, through its unique mode of action potentiates beneficial endogenous vasoactive peptides via NEP inhibition while inhibiting the Renin Angiotensin System (RAS) via angiotensin II type 1 receptor blockade. Consistent with this mechanism of action, the recently completed landmark randomized trial (PARADIGM-HF, N=8442) demonstrated that LCZ696 was superior to enalapril (current standard of care) in reducing cardiovascular (CV) death and heart failure hospitalization in patients with HFrEF. The magnitude of these advantages of LCZ696 over an angiotensin converting enzyme (ACE) inhibitor was statistically significant and clinically relevant, particularly since the drug was compared with current standard of care with an established mortality benefit in HF patients (McMurray et al 2014). In this study, compared with enalapril (ACEI), LCZ696 demonstrated a 20% risk reduction for HF hospitalization or CV death (primary endpoint, p = 0.0000002), 20% risk reduction in CV death alone (p=0.00004), and 21% risk reduction in HF hospitalization alone (p=0.00004), In addition, LCZ696 also demonstrated great benefit in symptom improvement, total HF hospitalization, all cause hospitalization and emergency room visits compared to enalapril.

The mechanism of action of LCZ696 suggests that it also may impact the suspected pathophysiology of HFpEF. In the Phase 2 PARAMOUNT study, 12 weeks of treatment with LCZ696 resulted in a significant reduction in N-terminal pro-brain natriuretic peptide (NT-ProBNP) and the reduction was sustained at 36 weeks. Reductions in NT-proBNP have been

[redacted]

associated with improved outcomes in patients with heart failure (Masson et al 2008). NYHA class improved significantly and significant reductions in echocardiographic parameters of left atrial size were seen at 36 weeks supporting the hypothesis that LCZ696 might alter the pathophysiology and natural course of disease in HFpEF. LCZ696 was well tolerated in the completed Phase 2 trial in patients with HFpEF (PARAMOUNT) and Phase 3 trial in patients with HFrEF (PARADIGM-HF) with a safety profile similar to that of comparators.

Patients will be instructed not to take any RAS blockade medications (ACEi, ARB or renin inhibitor) on the day they start treatment run-in study drug to avoid excess RAS blockade. Concomitant ACEi or ARB will be replaced by study medication (valsartan). All patients will continue to receive RAS therapy (valsartan or LCZ696) for the entire study duration. All patients will be allowed to continue receiving the rest of their background CV medications. The patient should be on an optimal medical regimen of diuretics and background medications to effectively treat comorbidities, such as hypertension, diabetes mellitus, atrial fibrillation, and coronary artery disease.

PET scanning involves intravenous administration of radiotracers, but the exposure to radiation is very minimal as the dose of approximate 10 millicuries radiation is received at each PET scanning visit. Florbetapir ^{18}F, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure.

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring.

Neprilysin (neutral endopeptidase or NEP) is one of several proteases capable of degrading Aβ. Although the relative contribution of neprilysin to Aβ clearance in humans is not understood, the potential exists for Aβ levels to be altered by inhibition of neprilysin. The clinical significance of this is unknown. Altered clearance of brain Aβ peptide has been suggested as a potential mechanism in the pathogenesis of Alzheimer's disease. Short term administration of LCZ696 400 mg once daily in healthy subjects for 14 days did not result in changes in CSF Aβ40 and Aβ42 concentrations, despite having measurable concentrations of LBQ657 (neprilysin inhibitor moiety of LCZ696) in the CSF relevant for neprilysin inhibition. The clinical relevance of the increase in CSF Aβ38 observed with LCZ696 is unknown. These observations suggest that enzymes and disposition pathways other than neprilysin appear to be more important in the clearance of CSF Aβ in humans. Currently available data do not suggest that LCZ696 treatment in humans results in meaningful increases in CSF Aβ. In clinical studies where patients with heart failure have been treated with LCZ696 for up to 4.5 years, there was no increase of incidence of AD or dementia-related adverse events, though none of these studies was designed to evaluate the effect of LCZ696 on AD or dementia.

In a large retrospective study it was observed that use of ACE inhibitors was associated with improvements in cognitive performance in patients with heart failure (Zuccala et al 2005). Similarly data from a small randomized trial indicate that in elderly hypertensive patients treatment with valsartan may be associated with improvement in some components of cognitive function (Fogari et al 2004). Although the long-term effects of treatment with LCZ696 on cognitive performance remains unknown, it is possible that an improvement in cardiovascular function as a result of treatment with LCZ696 might benefit cognition in patients with heart failure.

[redacted]

Since this is a long-term study, participating patients will benefit from careful monitoring and follow-up during the entire study duration regardless of whether they are receiving the study medication. In addition, patients can visit their doctors at an unscheduled visit as necessary.

4 Population

The study population will consist of male and female patients (≥ 60 years old) with chronic symptomatic HF (NYHA class II-IV). Eligible patients are those with the symptoms of HF, LVEF > 40%.

The goal is to randomize a total of approximately 520 patients in more than 100 centers worldwide. With an expected screening and run-in failure rate of approximately 40%, it is estimated that approximately 870 patients will be screened.

A subset of about 430 randomized patients will be enrolled in the amyloid PET imaging substudy.

4.1 Inclusion criteria

To be eligible for inclusion in this study, patient must fulfill all of the following criteria:

1. Written informed consent including consent for APOE4 gene testing must be obtained before any assessment is performed.
2. Male or female patients aged ≥60 years of age.
3. Chronic heart failure with current symptom(s) (NYHA class II-IV) at Screening visit.
4. LVEF >40%
    a. By any method using most recent assessment within 6 months prior to screening visit. OR
    b. By an echocardiogram performed during the Screening visit, if previous assessment is not available.
5. NT-proBNP ≥ 125 pg/mL at Screening visit
6. Patient with evidence of adequate functioning (e.g.: intellectual, motor, visual and auditory) to complete the study assessments and has elementary education or 6 years of sustained employment.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Current acute decompensated HF requiring augmented therapy with diuretics, vasodilators and/or inotropic drugs. If hospitalized for any medical conditions including heart failure patients should be clinically stable and be discharged from hospital for at least 2 weeks prior to screening.
2. Acute coronary syndrome (including myocardial infarction (MI)), cardiac surgery, other major CV surgery, or urgent percutaneous coronary intervention (PCI), carotid surgery or

[redacted]

carotid angioplasty, history of stroke or transient ischemic attack within the 3 months prior to Screening visit or an elective PCI within 30 days prior to Screening visit.

3. Patients with history of hereditary or idiopathic angioedema or angioedema related to previous ACEi or ARB therapies.
4. Patients with one of the following:
   a. Patients with serum potassium >5.2 mmol/L (mEq/L) at Screening visit
   b. Patients with serum potassium >5.4 mmol/L (mEq/L) at any visit during run-in treatment period or at randomization visit
   c. Systolic blood pressure (SBP) ≥180 mmHg at Screening visit, **or**
   d. SBP <110 mmHg at Screening visit, **or**
   e. SBP <100 mmHg or symptomatic hypotension as determined by the investigator at Visit 103 or at randomization visit
   f. Body mass index (BMI) >45 kg/m^2
5. Patients who require treatment with 2 or more of the following: an ACEi, an ARB or a renin inhibitor.
6. Patients with
   a. known pericardial constriction, genetic hypertrophic cardiomyopathy, infiltrative cardiomyopathy or
   b. hemodynamically significant obstructive valvular disease.
7. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 beats per minute.
8. Evidence of hepatic disease as determined by any one of the following: SGOT (aspartate aminotransferase (AST)) or SGPT (alanine aminotransferase (ALT)) values exceeding 3 x the upper limit of normal (ULN), bilirubin >1.5 mg/dl at screening visit.
9. Patients with one of the following:
   a. eGFR <30 mL/min/1.73m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) formula at Screening visit, **or**
   b. eGFR <25 mL/min/1.73m^2 at Visit 103 or at end of run-in/randomization visit, **or**
   c. eGFR reduction >35% (compared to Visit 1) at Visit 103 or Visit 199/201
10. Presence of known functionally significant bilateral renal artery stenosis
11. MMSE score <24 at screening visit
12. Patients with a clinical diagnosis of Alzheimer's disease or other dementia syndromes or any indication for or current treatment with cholinesterase inhibitors and/or another prescription AD treatment (e.g. memantine).
13. Any history of medical or neurological condition likely to affect the participant's cognition (e.g., clinically significant brain trauma with loss of consciousness >3 minutes within 6 months prior to screening, Huntington's disease, Parkinson's disease, Lyme's disease, syphilis, HIV dementia, uncontrolled seizure disorder) or clinically significant abnormalities in thyroid function tests, Vitamin B12 or folate deficiency requiring treatment at screening (Patients who are adequately treated may be included at investigator discretion).

[redacted]

14. Inability to perform cognitive battery or other study evaluations based on significant motor (e.g. hemiplegia, muscular-skeletal injury) or sensory (blindness, decreased or uncorrected visual or auditory acuity) skill.
15. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.
16. Clinically significant cerebral pathology, for example large cerebral aneurysm, space occupying lesion etc. that may impact cognition as assessed by MRI central reader.
17. Any contraindication or intolerance to MRI or PET investigations (with fluorinated radiopharmaceuticals), including but not limited to: presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI.
18. Previous or planned Nuclear Medicine Radiology research that will exceed the dosimetry acceptable exposure in the country, when adding the scheduled study PET scans.
19. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
20. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury within the last 5 years
21. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
22. History of non-compliance to medical regimens and patients who are considered potentially unreliable.
23. History or evidence of drug or alcohol abuse within the last 12 months
24. History or presence of any other disease with a life expectancy of <3 years
25. Women of child bearing potential defined as all women physiologically capable of becoming pregnant. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
26. Persons directly involved in the execution of this protocol
27. Use of other investigational drugs at the time of enrollment, or within 30 days, or within 5 half-lives of enrollment, whichever is longer.
28. Patients who previously received treatment with LCZ696.
29. Patients who are on current treatment with sedative hypnotics, selective serotonin re-uptake inhibitors (SSRIs, e.g. paroxetine, sertraline, citalopram, escitalopram), serotonin

[redacted]

norepinephrine re-uptake inhibitors (SNRIs, e.g. venlafaxine, duloxetine), atypical antipsychotics, and low dose tricyclic anti-depressants should be on a stable regimen (defined as no change to the participant's medication intake pattern rather than adherence to the prescribed regimen) for at least 12 weeks prior to screening.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The sponsor will provide the following study drugs:

Single-blind treatment run-in period

All eligible patients will enter a treatment run-in epoch where they will receive valsartan followed by LCZ696.

The following study drugs will be provided:

- Valsartan 40 mg and 80 mg tablets
- Placebo to match valsartan 40 mg and 80 mg tablets
- LCZ696 50 and 100 mg tablets
- Placebo to match LCZ696 50 mg and 100 mg tablets

The use of an ACEi, ARB or renin inhibitor in addition to study drug during the treatment run-in epoch is strictly prohibited.

Randomized treatment period

All eligible patients will be randomized to either LCZ696 200 mg bid (dose level 3) or valsartan 160 mg bid (dose level 3). In addition, patients will continue to take optimal background therapy to treat co-morbid conditions, as considered appropriate by the investigator and in accordance with local standard, with the exception of an ACEi or ARB as this will be replaced by study drug. The use of an open-label ACEi, an ARB or renin inhibitor in addition to randomized study drug is strictly prohibited.

The following study drugs will be provided:

- LCZ696 50 mg, 100 mg and 200 mg tablets
- Placebo to match LCZ696 50 mg, 100 mg, and 200 mg tablets
- Valsartan 40 mg, 80 mg and 160 mg tablets
- Placebo to match valsartan 40 mg, 80 mg, 160 mg tablets

In some countries where LCZ696 is approved the 50, 100 and 200 mg doses of LCZ696 are referred as 24/26 mg (sacubitril/valsartan), 49/51 mg (sacubitril/valsartan) and, 97/103 mg (sacubitril/valsartan), respectively.

All study medications will be supplied in bottles. Sufficient medication will be provided for the treatment according to study protocol, including additional medication to allow for

[redacted]

delayed visits. Medication labels will be in the local language and comply with the legal requirements of the country. They will include storage conditions for the drug and the medication number, but no information about the patient.

5.1.2 Additional treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

Patients will be assigned to one of the following two treatment arms in a ratio of 1:1 at the randomization visit.

- LCZ696 200 mg bid
- Valsartan 160 mg bid

5.3 Treatment assignment and randomization

At Visit 199, patients will be scheduled to undergo a PET scan. PET scan images will be centrally read by the imaging vendor to classify a patient as amyloid positive or amyloid negative. Patients will be stratified at Visit 201 according to their amyloid status within 3 to 5 days after acquisition of the baseline PET image. The investigator will remain blinded to the amyloid status. Since it may take several days to obtain results, it is recommended that the site take this into consideration when scheduling Visit 201, while keeping the patient on study medication. All eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by three factors, age (<75, ≥75 years old), MMSE summary score at baseline (<28, ≥28), and brain amyloid status (unknown, amyloid (+) or amyloid (-)). Note that patients who do not participate in the PET imaging sub-study will be classified as having unknown amyloid status.

The randomization scheme for patients will be reviewed and approved by a member of the Novartis Randomization Group.

[redacted]

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study with the following exceptions:
  1. The independent and unblinded statistician, programmer and data personnel who are involved in preparing safety review reports for the Data Monitoring Committee (DMC). These personnel will not be involved in any other trial conduct related activities.
  2. The DMC members who review the interim safety data.
- The identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.
- A double-dummy design is used because the identity of the investigational treatment cannot be disguised due to their different forms.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9), at the time of safety and efficacy data review by the DMC and at the conclusion of the study. An assessment will be done by the appropriate site personnel and the Medical Lead (or designee) after treatment code break and the patient must discontinue the study treatment.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed of the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form (ICF), the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site should select the Case Report Form (CRF) book with a matching Subject Number from the Electronic Data Capture (EDC) system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening Disposition CRF. Patients that take treatment run-in study drug and are not randomized are considered run-in failures. The reason for failure to randomize will be entered on the Run-in Disposition CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

[redacted]

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment arms and a dose level. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Novartis will supply the investigators with all study medications required for the course of the study. Patients will be provided with medication packs containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled office visit. In order to adequately blind the study, patients will be required to take a total of two tablets (one tablet from the LCZ696/LCZ696 matching placebo pack and one tablet from the valsartan/valsartan matching placebo pack) twice a day for the duration of the study. Table 5-1 summarizes the study drug that will be taken during the run-in epoch and Table 5-2 summarizes the study drug that will be taken during the randomized treatment epoch.

[redacted]

Table 5-1 Study drug dispensed for the treatment run-in epoch by study visit

Study visit	Dose level	LCZ696	Valsartan
101[a]	1	50 mg matching placebo bid	40 mg bid
102	2[a]	100 mg matching placebo bid	80 mg bid
103	2[a]	100 mg bid	80 mg matching placebo bid

[a] Investigators may consider initiating treatment on dose level 2 (valsartan 80 mg bid and 100 mg matching placebo bid) at Visit 102 (see Figure 3-2) in those patients being treated with at least the minimum dose of ACEi or ARB at Visit 1 (see Table 3-1); bid – twice daily dosing

Table 5-2 Study drug dispensed during the randomized treatment epoch by study visit

Study visit	Dose level	LCZ696	Valsartan
201	3[a]	200 mg or matching placebo bid	160 mg or matching placebo bid
Available for any visit after Visit 201	2[b]	100 mg or matching placebo bid	80 mg or matching placebo bid
Available for any visit after Visit 201	1[c]	50 mg or matching placebo bid	40 mg or matching placebo bid

[a] This dose level must be maintained for as long a duration as possible. If down-titration is necessary due to side effects, the patient should be re-challenged as soon as medically possible per the investigator's judgment.
[b] Only if dose level 3 is not tolerated despite modification of other concomitant medications.
[c] Only if dose levels 2 or 3 are not tolerated despite modification of other concomitant medications.
bid – twice daily dosing

Patients will be instructed to take their morning study drug doses between 06:00 and 09:00 (6-9 AM) and their evening study drug doses between 18:00 and 21:00 (6-9 PM). The study drugs should be taken with water, with or without food. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return to his/her regular study drug administration schedule.

All kits of investigational treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator should promote compliance by instructing the patient to take the study drug treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose level adjustments and interruptions of study treatment are permitted in order to keep the patient on study drug. The following guidelines should be followed:

Every attempt should be made to maintain patients at the target study drug dose level throughout the trial. If the patient cannot tolerate the target study drug dose level, the investigator should consider adjusting or stopping concomitant background medications for co-morbid conditions, before considering down titration to the next lower dose level of study

[redacted]

drug. For hypotension or dizziness, consideration should be given to reducing the dose or to stopping concomitant medications that lower BP, or reducing the dose of diuretic.

There are three dose levels of study medication (both LCZ696 and Valsartan) as depicted in Table 5-2 with target dose level as '3'. Two other dose levels (dose level 1 and 2) are available for down-titrating the patient depending on the clinical need and investigator's discretion.

The target dose level for this study is LCZ696 200 mg bid and valsartan 160 mg bid (Dose level 3).

Adjustment of study drug dose level

If despite adjustment of concomitant medications per the guidance provided and the situation is not being corrected, then the investigator may consider down titrating the study drug dose level according to the following instructions:

During the randomized treatment epoch, down titration of the study drug at any time based on the judgment of the investigator will be allowed according to the safety and tolerability criteria defined in Appendix 3, Appendix 4, and Appendix 5. If down titration is necessary, the patient should be down titrated to the next lower study drug dose level (Table 5-2). The patient may continue receiving the lower dose level for a recommended period of 1 to 4 weeks before being re-challenged at the next higher dose level. For example, a patient who encounters tolerability problems at the dose level 3 (the target study drug dose level), should receive the study drug at dose level 2 for 1 to 4 weeks at the discretion of the investigator. Then, he/she should be re-challenged with up-titration back to dose level 3.

If the tolerability issues are not alleviated despite down titration by one dose level, the investigator may down titrate further to the next lower study drug dose level for 1 to 4 weeks, up to temporary discontinuation of the study drug. Again, once stable, the patient should be re-challenged with up titration to the next higher dose level every 1 to 4 weeks in an attempt to bring back the patient gradually to dose level 3 (the target study drug dose level). The investigator may choose the next dose level for down- or up-titration according to his or her judgment (Table 5-2). As discussed in Section 5.5.4, the IRT system should be contacted to register any changes in the patient's study drug dose level, including in cases of temporary and permanent discontinuation of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study drug dose level.

In some instances, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow any further up titration to the target dose level of study drug (dose level 3). In this case, it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level by the patient. The adjustment of the study drug dose levels must be recorded on the Dosage Administration Record CRF.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those patients who temporarily discontinue it as soon as medically justified in the opinion of the investigator.

[redacted]

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate dose level (Table 5-2) per his/her medical judgment. If tolerated, the patient should be up-titrated to a dose level every 1 to 4 weeks to the target dose level 3, as per the investigator's judgment. Should the patient not tolerate the re-start study drug dose level, he/she may be down-titrated again (if appropriate) or temporarily discontinue the study medication again and a new attempt to up-titrate or reintroduce the study drug could be considered by the investigator as soon as medically justified in his/her judgment.

The use of an open-label ACEi, ARB or a renin inhibitor is strongly discouraged while patient is off study drug. However, if for any reason a patient off study drug has started open-label treatment with an ACEi it must be discontinued ≥36 hours prior to restarting study drug. For patients off study drug treated with an ARB or a renin inhibitor it must be discontinued prior to re-initiation of study drug (Table 5-3).

These changes must be recorded on the Dosage Administration Record CRF.

In case of pregnancy discovered during the screening or run-in epochs or during double-blind epochs, the patient will be withdrawn from the study immediately.

See Section 7.7 for further details on pregnancies and reporting guidelines.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension, and renal dysfunction will be provided to investigators (Appendix 3, Appendix 4, and Appendix 5 respectively). Patients may receive open-label ACEis, ARBs or a renin inhibitor during the study ONLY if the study drug has been temporarily or permanently discontinued. If for any reason a patient off study drug has started open-label treatment with an ACEi it must be discontinued ≥36 hours prior to restarting study drug.

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient is enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

Drugs known to affect cognition:

Initiation of cholinesterase inhibitors or other prescription, AD treatments, anti-depressant or psychotropic medication should be documented in the concomitant medication page. The

[redacted]

relevant follow up questionnaire CRF page should be completed providing detail of the indication for initiation of such therapies and the clinical investigations and diagnosis.

Sedative hypnotics may be allowed if participants are currently on a stable regimen (defined as no change to the participant's medication intake pattern rather than adherence to the prescribed regimen) for at least 12 weeks prior to screening. If initiated during study these must be withheld for 72 hours unless maintained on a stable regimen for 6 weeks prior to scheduled cognitive assessment.

Selective serotonin re-uptake inhibitors (SSRIs, e.g. paroxetine, sertraline, citalopram, escitalopram), serotonin norepinephrine re-uptake inhibitors (SNRIs, e.g. venlafaxine, duloxetine), atypical antipsychotics, and low dose tricyclic antidepressants are allowed provided participants are currently treated with a stable regimen for at least 12 weeks prior to screening.

Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements, mineralocorticoid receptor antagonist (MRA) and any other medications known to raise potassium levels should be used with caution while the patient is receiving the study drug due to the increased possibility of occurrence of hyperkalemia. The investigator is encouraged to assess patients' potassium levels regularly, especially in those who are receiving these medications.

Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors should be used with caution while the patient is receiving study medication due to the increased possibility of the occurrence of hypotension.

Nesiritide and intravenous (IV) nitrates

The concomitant administration of LCZ696 with nesiritide and IV nitrates has not been studied. In the event a study patient requires the concomitant administration of nesiritide and/or IV nitrates with the study medications, the investigator should consider starting them at a lower dose or slower infusion rate while monitoring the patient's BP carefully.

HMG-CoA reductase inhibitors

Caution is recommended when co-administering LCZ696 with statins because of the potential to raise plasma statin levels.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-3 is NOT allowed after the start of study drug due to safety reasons, unless the actions specified are taken.

Table 5-3 Prohibited treatment

Medication	Action to be taken
Any ACEi	Discontinue study drug. The open label ACEi must be stopped for ≥36 hours prior to re-initiation of study drug
Any ARB	Discontinue study drug. The open label ARB must be stopped prior to re-

[redacted]

Medication	Action to be taken
	initiation of study drug
Any Renin inhibitor	Discontinue study drug. The open label renin inhibitor must be stopped prior to re-initiation of study drug

ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

ACEis, ARBs and renin inhibitors

The concomitant use of open-label ACEis, ARBs or a renin inhibitor is strictly prohibited while the patient is receiving study drug. If there is a strong need for open label use of ACEi, ARB or renin inhibitor, then study drug must be temporarily discontinued. If the patient is to be started on open-label ACEi, the study drug must be stopped for ≥36 hours prior to initiating ACEi. The same is true for restarting the study medication for those patients who are on open label ACEi therapy. ARBs or a renin inhibitor should be stopped prior to resuming study drug.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and the Medical Lead (or designee) after an emergency treatment code break and the patient must discontinue the study treatment.

[redacted]

5.6 Study Completion and Discontinuation

5.6.1 Study completion and post-study treatment

At the end of the study, all patients will return for the final end of study (EOS) visit (Visit 299) and be asked to return the remaining study drug. The study will be completed once all assessment up to the last participant reaches Month 36 (Visit 299) **or** a recommendation is made by the DMC to prematurely stop the study.

The study will be complete when the last patient enrolled has completed their last visit.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment occurs when study drug is stopped earlier than the protocol planned duration, and this can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.9 and Section 7.7)
- Use of prohibited treatment as per recommendation in Table 5-3
- Any situation in which study participation might result in a safety risk to the patient

However; study treatment discontinuation does not constitute withdrawal from the study and should not lead to the patient being withdrawn from the study.

Every effort should be made to complete end of treatment (EOT) assessments within 3 months of the last study drug dose for patients who have discontinued study drug permanently. For patients who terminate the study early, they are expected, and should be encouraged, to attend all the protocol specified study visits and perform all measurements as stipulated in the visit schedule (Table 6-1) and remain in follow up for the duration of the trial.

If they fail to return for these assessments for unknown reasons, every effort should be made to contact them. If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

The investigator must contact the IRT to register the patient's discontinuation from study treatment and must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF.

The emergence of the following circumstances will require permanent study drug discontinuation:

[redacted]

- Withdrawal of informed consent
- Investigator thinks that continuation would be detrimental to the patient's well-being
- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator

Use of an open label ACEi, ARB or renin inhibitor will require temporary or permanent discontinuation (study drug may be restarted once these medications are stopped).

Study drug may be discontinued at the investigator's discretion if any of the following occurs:

- Any severe suspected drug-related AE
- Any other protocol deviation that results in a significant risk to the patient's safety.

The appropriate personnel from the site and Novartis will assess whether study drug should be permanently discontinued for any patient whose treatment code has been broken inadvertently for any reason.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

The details about study assessment to be completed for patients who permanently discontinued study drug are provided in Section 6.

5.6.3 Withdrawal of informed consent

Patients/subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1.

[redacted]

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit-risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

After randomization, study drug discontinuation (permanent or temporary) for any reason does not constitute withdrawal from the study and should not lead to the patient being withdrawn from the study. Patients who discontinue study drug should be requested to return for an End of Treatment visit (EOT) in which all of the assessments outlined in Table 6-1 will be performed.

Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the end of study visit will be performed. At the end of study visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Every effort should be made to complete end of treatment (EOT) assessments within 3 months of the last study drug dose for patients who have discontinued study drug permanently. Patients who terminate study drug early are expected, and should be encouraged to, attend all the remaining protocol specified study visits and perform all measurements as stipulated in the visit schedule (Table 6-1).

For EOT / End of Study (EOS) visit, the PET and MRI scans will only be performed if prior scans were performed more than twelve months ago. The CCB, [redacted] FAQ, [redacted] assessments will only be performed if prior assessments were performed more than three months ago.

Documentation of attempts to contact the patient should be recorded in the source documentation.

[redacted]

After identifying a potential patient, an informed consent form (ICF) must be signed by the patient before performing all study-related screening. The AE and serious adverse event (SAE) reporting period begins at the time the ICF is signed.

A Visit 199 (end of run-in visit) will be completed for all patients who enter the treatment run-in epoch. For patients who discontinue during the treatment run-in epoch or who are not able to be randomized due to safety reasons, Visit 199 will be their discontinuation visit.

For patients that will be randomized, Visit 199 will be their end of treatment run-in disposition visit. [redacted] In addition, NYHA class assessment, concomitant medications, review of inclusion/exclusion criteria, drug accountability, AE/SAE, should also be done at Visit 199. To allow patients to be randomized at Visit 201, patients should have a PET scan scheduled at Visit 199 (for all patients participating in the substudy) since it may take up to 5 days following the scan for the brain images to be centrally read. PET scan should be scheduled only after confirming that the patient fulfills all inclusion and exclusion criteria, safety criteria and is eligible for randomization.

Following completion of the PET scan, all patients will be randomized at Visit 201. The CogState Cognitive Battery, [redacted] FAQ, APOE4, and plasma beta-amyloid assessments will all be performed at Visit 201.

End of run-in assessments (Visit 199) and assessments for randomization (Visit 201) are reflected at Visit 199/201 in Table 6-1.

Visit 201 will be considered the reference visit for all study visits during the randomized treatment epoch. Regardless of the occurrence of any unscheduled visits, scheduled visits should be performed within the specified timeframe in relation to Visit 201 as outlined in Table 6-1. If a visit is completed earlier than scheduled or postponed, it should not result in the next visit being brought forward or postponed.

Patients will have regular clinic visits performed for the first 6 months (up to and including Week 26). Thereafter, patients will have clinic visits alternating with telephone contact visits every 3 months.

Patients/subjects will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

[redacted]

Table 6-1 Assessment schedule

Epoch		Screening	Active Run-in			Randomized Treatment													
Visit		1	101	102	103	199/ 201††	202	203	204[1]	205	206[1]	207	208[1]	209	210[1], 212[1]	211	EOT[3]	UNS	299[7] End of Study
Week (w)		-11/-7	-8/-4	-6/-3	-4/-2	0	13	26	39	52	65	78	91	104	117, 143	130			156
Month							3	6	9	12	15	18	21	24	27, 33	30			36
Informed consent	DS	X																	
Inclusion/Exclusion criteria	DS	X	X	X	X	X													
Safety monitoring criteria	DS	X		X[8]	X	X													
Demography/Relevant Medical history/Current medical conditions	DS	X																	
Heart Failure/ Smoking history/Alcohol history	DS	X																	
Echocardiography[4]	DS	X																	
Concomitant medications	DS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA classification (HF signs/symptoms)	DS	X				X		X		X		X		X		X	X	X	X
Florbetapir ^{18}F PET scan	DS					X[λ]						X					X[5]		X[5]
MRI Scan[15]	DS	X										X					X[5]		X[5]
Cognitive Assessment (CogState Battery)[6,12]	DS	X			X	X[λ]		X		X		X		X		X	X		X
[redacted]																			

[redacted]

Epoch		Screening	Active Run-in			Randomized Treatment													
Visit		1	101	102	103	199/ 201††	202	203	204[1]	205	206[1]	207	208[1]	209	210[1], 212[1]	211	EOT[3]	UNS	299[7] End of Study
Week (w)		-11/-7	-8/-4	-6/-3	-4/-2	0	13	26	39	52	65	78	91	104	117, 143	130			156
Month							3	6	9	12	15	18	21	24	27, 33	30			36
Functional Activity Questionnaire (FAQ)[6]	DS	X				Xλ		X		X		X		X		X	X		X
Physical Exam[9]	S	X		X	X	X		X		X		X		X		X	X	X	X
[redacted]																			
Height	DS	X																	
Weight	DS	X				X		X		X		X		X		X	X	X	X
[redacted]																			
Abbreviated laboratory evaluations[10]	DS			X[8]	X		X	X				X				X		X	
Local laboratory[11]				(X)	(X)	(X)												(X)	
Vitamin B12 and Folate	S	X																	
Thyroid stimulating hormone	S	X																	
FSH[2]	S	X																	
APOE4 genotyping/ [redacted][13]	DS					X													
NT-proBNP[14]	DS	X																	
Dispense study medication	S		X	X	X	Xλ	X	X		X		X		X		X		(X)	
Contact IVRS	S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Accountability	DS			X	X	X	X	X		X		X		X		X	X	(X)	X
[redacted]																			
Plasma β-amyloid[16]	DS	X				Xλ	X			X				X			X		X

[redacted]

Epoch		Screening	Active Run-in			Randomized Treatment													
Visit		1	101	102	103	199/ 201††	202	203	204[1]	205	206[1]	207	208[1]	209	210[1], 212[1]	211	EOT[3]	UNS	299[7] End of Study
Week (w)		-11/-7	-8/-4	-6/-3	-4/-2	0	13	26	39	52	65	78	91	104	117, 143	130			156
Month							3	6	9	12	15	18	21	24	27, 33	30			36
Screening disposition	DS	X																	
Run-in disposition	DS					X													
Treatment disposition	DS																X		X

DS= assessment to be recorded in clinical database; S= assessment to be recorded on source document; UNS = unscheduled visit;
EOT=(end of treatment); Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment
(X) = optional assessment
††= Visit 199/201 (end of treatment run-in) will be completed for all patients who enter the treatment run-in epoch. For patients who discontinue during the treatment run-in epoch, Visit 199 will be their discontinuation visit. For patients that have completed a PET scan and are randomized at Visit 201, procedures marked as 'λ' will be performed.
[1] Telephone visit
[2] Female subjects only with oophorectomy without hysterectomy.
[3] If patient discontinues study drug permanently these assessments should be done within 3 months of last dose.
[4] Qualifying LVEF measurements/documentation will be based on locally obtained most recent assessments performed ≤ 6 months prior to Visit 1. If an EF assessment performed ≤ 6 months prior to Visit 1 is not available, an echo must be performed during the Screening epoch.
[5] The PET and MRI scans will be done at EOT/EOS only if prior scans were performed more than twelve months ago.
[6] The CCB, [redacted] FAQ, [redacted] will be done at EOT/EOS only if prior assessments were performed more than three months ago
[7] Visit 299 (end of study visit) will be completed for all patients that enter the randomized treatment epoch.
[8] Serum potassium and eGFR to be performed at Visit 102 only if patient enters the run-in epoch at Visit 101.
[9] Complete physical exam will be performed at Screening Visit 1, EOS, and EOT, all other visits will be a short physical exam.
[10] Abbreviated laboratory assessments includes: serum creatinine, potassium and eGFR
[11] Serum potassium and serum creatinine for eGFR. If patient enters run-in period at Visit 102, laboratory evaluation at this visit is not required
[12] Cognitive assessments should ideally be administered by the same assessor in a quiet environment and prior to any other clinical assessments scheduled during the day
[13] If the PG sample is not collected at Visit 201, it may be obtained at any visit thereafter and is only analyzed in patients consenting to the PG analysis
[14] NT-proBNP will be analyzed in serum and collected as part of the clinical chemistry sample
[15] MRI scans at Visit 207 and Visit 299 are performed only in patients participating in the PET substudy
[16] Plasma β-amyloid will be assessed only in patients participating in the PET substudy

[redacted]

Epoch		Screening	Active Run-in			Randomized Treatment													
Visit		1	101	102	103	199/ 201[††]	202	203	204[1]	205	206[1]	207	208[1]	209	210[1], 212[1]	211	EOT[3]	UNS	299[7] End of Study
Week (w)		-11/-7	-8/-4	-6/-3	-4/-2	0	13	26	39	52	65	78	91	104	117, 143	130			156
Month							3	6	9	12	15	18	21	24	27, 33	30			36
	AE – adverse event; APOE4 – Apolipoprotein E ε4 allele; [redacted]; EOT – end of treatment; FSH – follicle stimulating hormone; IVRS – interactive voice recognition system; [redacted] NT-proBNP – N-terminal pro-brain natriuretic peptide; NYHA – New York Heart Association; PET – positron emission tomography; SAE – serious adverse event																		

[redacted]

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next epoch will have the study completion page for the Screening epoch, demographics, inclusion/exclusion, [redacted] data collected. [redacted].

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity and source of patient referral. A detailed medical history (including HF, CV and other conditions relevant to the study population to be enrolled), smoking and alcohol history, and current medical conditions present before the signing of the informed consent will be collected.

MMSE and Echocardiography will be done at screening to determine eligibility for inclusion in to the study.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the care giver. This information should be captured in the source document at each visit. The investigator and/or study personnel should counsel the patient if compliance is below 80% at any time during the study. Study drug accountability will be determined by the site monitor while performing routine site visits and at the completion of the study.

The duration of randomized treatment exposure will be calculated based upon the start and stop dates recorded in the dosage administration record (DAR) eCRF.

6.4 Efficacy

6.4.1 Cognitive function assessment by CCB

The primary endpoint will be change in GCCS from baseline (Visit 201/randomization) to 3 years defined from performance on the seven tasks from the CogState cognitive battery.

1. The Detection test (DET) is a simple reaction time paradigm shown to assess psychomotor function.
2. The Identification test (IDT) is a choice reaction time paradigm shown to assess visual attention.
3. The Continuous Paired Associate Learning (CPAL) visual pattern paradigm shown to assess visual episodic memory.
4. The One Back Test (ONB) is a n-back paradigm shown to assess working memory.

[redacted]

5. International Shopping List Test (ISLT) is a verbal list learning paradigm shown to assess verbal learning.
6. The International Shopping List Test delayed recall (ISLT-DR) is a delayed recall condition from a verbal list learning paradigm shown to assess verbal memory.
7. The Groton Maze Learning Test (GMLT) is a hidden pathway maze learning paradigm shown to assess executive function.

The individual cognitive functions measured by the CogState cognitive battery can be organized into three main cognitive domains;

1. Attention: defined by performance on the Detection, and Identification tests
2. Episodic Memory: defined by performance on the CPAL, ISLT and, ISLT-DR
3. Executive function: defined by performance on the GMLT and ONB test

Performance across these three domains can then be organized to provide a measure of general cognitive function.

These individual cognitive functions and their related cognitive domains have been selected for the current study on the basis that they have been shown to be relevant to characterizing the cognitive impairment that can occur in patients with heart failure and underlying CV disease (Bauer et al 2011). They also have been shown to be associated with both absolute levels of amyloid and rates of changes in amyloid deposition in older adults (Lim et al 2012). The cognitive test battery evaluates the most relevant cognitive domains associated with changes in brain Aβ and changes as a result of progressive CV disease.

The cognitive tests that will be utilized in this study exhibit appropriate sensitivity to detect changes that would occur in the early, prodromal stage of AD, especially in patients positive for amyloid (Lim et al 2014).

Each of the cognitive tests in the CCB will be administered electronically to patients using a computer or tablet in an area suitable for testing without distraction. While subjects themselves perform the tests on the computer or tablet, this performance is guided by an appropriately trained and credentialed rater. The electronic administration ensures standard administration of tests and also means that the CCB can be administered with high fidelity by non-expert but appropriately trained clinical staff (e.g., research assistants or nurses). Assessment with the CCB should take place in a location free from distraction and all site staff nominated to administer the CCB will undergo specific training to ensure that they understand the testing software, the testing processes, the administration of each test and the transfer of test results to CogState. Further details about CogState battery will be provided in CCB manual.

The cognitive test battery will be administered at Screening visit (Visit 1), Visit 103, and randomization visit (Visit 201), and throughout the duration of the study at 6 month intervals, including the end of treatment visit (if prior assessments were performed more than three months ago) and end of study visit (Visit 299).

[redacted]

6.4.2 Individual cognitive domains

Change from baseline in individual cognitive domains (memory, executive function, and attention) as assessed by composite z-scores by individual components of the cognitive assessment battery at 3 years will be evaluated.

[redacted]

6.4.4 Instrumental activities of daily living as assessed by functional activity questionnaire

The functional activities questionnaire will be used as a standardized assessment of activities of daily living. This questionnaire is typically used to distinguish normal subjects from subjects with mild to moderate cognitive impairment. FAQ evaluation will be performed at Screening visit (Visit 1), randomization visit (Visit 201), at 6 months (Visit 203), 12 months (Visit 205), 18 months (Visit 207), 24 months (Visit 209), 30 months (Visit 211), end of treatment visit (if prior assessments were performed more than three months ago), and at 36 months end of study (Visit 299). The changes from baseline to 3 years will be analyzed.

6.4.5 Appropriateness of efficacy assessments

6.4.5.1 Cognitive function assessment

The comprehensive battery of cognitive tests has been selected as the primary endpoint for this study as it will provide a measure of general cognitive function based on the performance in working memory, executive function, psychomotor speed, visual attention, visual episodic memory, verbal learning and delayed verbal recall.

The CogState Cognitive Battery (CCB) will be used to measure these cognitive domains because the performance measures from tests of these cognitive functions have been validated extensively, including in older patients with heart failure (Clark and McDougall 2006), healthy older individuals with increased levels of amyloid (Lim et al 2014) and in older patients with mild cognitive impairment and clinically classified dementia (Maruff et al 2013). Each test in the CCB has also been designed specifically for the repeated administration necessary in clinical trials in that they are brief to administer, reliable and that once they are learned, repeated administration is not associated with performance improvement, even over relatively short retest intervals (e.g. 1-hour) (Maruff et al 2013, Mielke et al 2014). This validity, brevity and repeatability has meant the performance on the CogState tests is sensitive

[redacted]

to true cognitive change (improvement or decline) in response to disease progression or treatment with pharmaceutical or surgical intervention in various disorders, diseases and injuries.

When considered together the measurement of cognitive function using the CCB enables optimal evaluation of any cognitive decline or cognitive improvement associated with LCZ696 treatment.

6.4.5.2 Individual cognitive domains

In addition to an overall cognitive function assessment using the GCCS, the three main cognitive domains comprising the GCCS, attention, memory, and executive function, will be further analyzed independently.

These individual cognitive functions and their related cognitive domains have been selected for the current study on the basis that they have been shown to be relevant to characterizing the cognitive impairment that can occur in patients with heart failure and underlying CV disease (Bauer et al 2011). They also have been shown to be associated with both absolute levels of amyloid and rates of changes in amyloid deposition in older adults (Lim et al 2012). The cognitive tests that will be utilized in this study exhibit appropriate sensitivity to detect changes that would occur in the early, prodromal stage of AD, especially in patients positive for amyloid (Lim et al 2014). The cognitive test battery evaluates the most relevant cognitive domains associated with changes in brain Aβ and changes that may occur as a result of progressive CV disease.

[redacted]

6.4.5.4 Instrumental activities of daily living as assessed by functional activity questionnaire

The functional activities questionnaire (FAQ) will be used as a standardized assessment of instrumental activities of daily living (IADL; Pfeffer et al 1982, Teng et al 2010). This questionnaire is typically used to distinguish normal subjects from subjects with mild to moderate cognitive impairment. The test is made up of 10 questions that reflect a subject's ability to perform activities of daily living and to function independently. Test scores range for 0 to 30, with a 0 score representing no impairment and a 30 score, as severely impaired. Each of 10 questions is scored from 0, representing normal to 3, dependent on someone else to perform the activity. The FAQ should be administered to the subject and will provide an assessment of patient's physical and social functioning.

[redacted]

6.5 Safety

[redacted] All additional information is de-identified prior to collection by Novartis or its agents.

6.5.1 Brain amyloid PET imaging

All imaging sites will be qualified by the imaging central lab. PET imaging will be performed at selected PET capable centers on all eligible patients participating in the substudy. Sites with patients performing the PET scan are a sub-set of the overall patient population and overall sites for the study. Every attempt should be made to perform the PET scans using the same scanner for an individual patient for the full duration of the study. PET scan images will be centrally read by the imaging vendor to classify a patient as amyloid positive or amyloid negative. Patients will be stratified at Visit 201 according to their amyloid status. The result of the amyloid status (positive or negative) will be blinded to investigators.

Brain amyloid PET scans will be performed at randomization visit (Visit 201), at 18 months (Visit 207), at the end of study visit (Visit 299) and at end of treatment visit. PET scanning will only be performed at 18 months, end of study or at the end of treatment visits if previous scans were performed more than twelve months ago. A key secondary endpoint will be change from baseline in the standardized uptake value ratio at 3 years. PET scanning will be performed with florbetapir ^{18}F / Amyvid®. Investigator ought to postpone PET scanning if currently experiencing an adverse event that could affect the PET scanning procedure or influence interpretation of the data.

Florbetapir ^{18}F will be manufactured at an approved facility and delivered to the participants as a bolus injection at the PET site. The target and maximum activity will be 370 ± 10% Megabecquerel (MBq)) at time of injection, though scanning will be permitted with a minimum of 185 MBq.

The approximate scanning time, during which the participants will be lying on his or her back in the PET camera, will be about 10 to 30 minutes. The total time required for each visit is expected to be less than 2.5 hours.

Patients will be supervised during each PET scan. After the PET scan has been completed, participants will be allowed to leave the PET center if there are no prohibitive findings or events, as assessed by a physician or the physician designate.

PET data will be analyzed to determine the composite cortical SUVr change during the study interval.

Details regarding image acquisition and data transfer by the scanning facilities, and the procedures, clinical assessments, and quantitative measurements performed by the core laboratory can be found in the Image Review and Technical Operations manuals.

[redacted]

[redacted]

6.5.3 Plasma beta-amyloid

Plasma β-amyloid (Aβ1-40) will be assessed in patients in the PET substudy from select centers. Blood samples will be processed as described in the laboratory manual. All samples will be given a unique sample number and a collection number (as listed in the blood log Sample log table). Plasma Aβ1-40 levels will be evaluated as change from baseline to pre-defined time points over a period of 3 years. While this provides mechanistic information about peripheral NEP inhibition the clinical relevance of changes in plasma β-amyloid are not known (Huang et al 2012). The results of plasma Aβ1-40 will be kept blinded as there is potential to unblind the treatment.

Blood samples for the determination of plasma Aβ1-40 will be collected at Screening (Visit 1) and at randomization (Visit 201), 3 months (Visit 202), 12 months (Visit 205), 24 months (Visit 209), EOT visit, and at end of study visit (36 months; Visit 299).

6.5.4 Cardiovascular events

The main purpose of this study is to assess the impact on cognitive function change and the rates of Aβ deposition over 3 years in patients receiving LCZ696 compared to valsartan. This study is not powered to detect treatment differences in cardiovascular events including CV death, HF hospitalization, stroke, MI. Therefore, these events will be collected as adverse events through the usual AE data collection mechanisms in this study. Investigators will record whether a hospitalization due to HF has occurred at each visit. Cause specific information about each death will also be collected (Section 7).

6.5.5 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes,

[redacted]

extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance [redacted]. A short physical exam will be conducted at all visits starting from Visit 102 except where a complete physical examination is required (see Table 6-1).

Information from all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded on the AE section of the CRF.

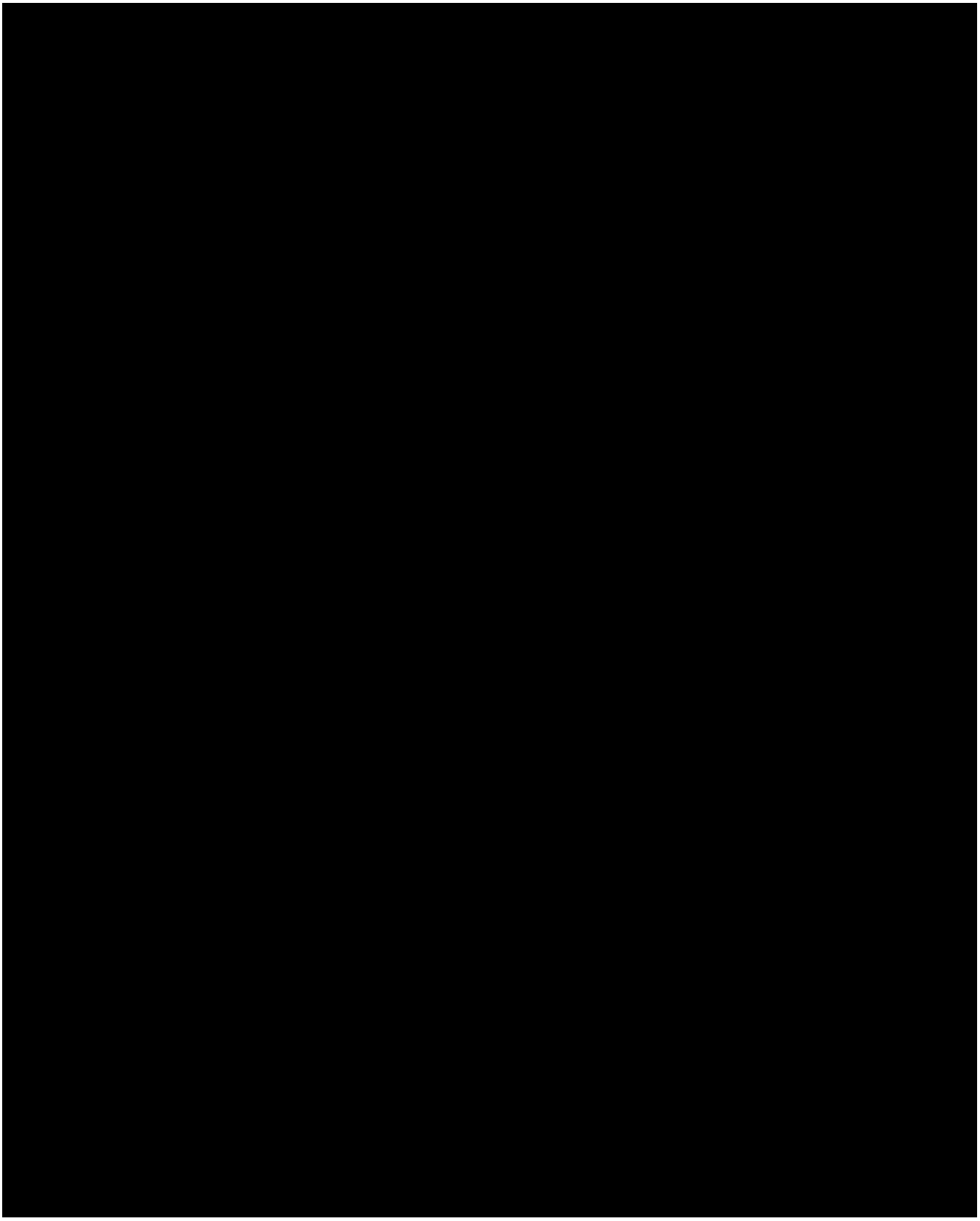
[redacted]

6.5.7 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

[redacted]

[redacted]



[redacted]

6.5.8.3 Plasma beta-amyloid

Plasma β-amyloid will be assessed in patients in the PET substudy from select centers. Blood sample for plasma β-amyloid will be taken at Visit 1 (screening), 199/201 (randomization), Visit 202 (Week 13), Visit 205 (Week 52), Visit 209 (Week 104), end of treatment (EOT), and Visit 299 (Week 156).

6.5.8.4 eGFR

Estimated eGFR will be calculated by the central or local laboratory using the following MDRD formula (Stevens et al 2006):

Estimated GFR (mL/min/1.73 m^2) = 175 × (standardized SCr in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 if female) or × (1.212 if black), where SCr is the standardized serum creatinine value.

6.5.8.5 APOE4 genotyping

The APOE4 gene has been identified as a genetic marker that predicts predisposition to cognitive decline and Alzheimer's disease (Corder et al 1993). To control for this predisposing factor, patients will be asked to provide blood samples for genotyping which will include assessment of their APOE4 genotype so that genetic predisposition is taken into account when assessing the cognitive function of the study participants. APOE4 genotyping will be done at Visit 199/201 in all patients. The sites will remain blinded to the APOE4 status during the study.

6.5.8.6 Other lab assessments

Other laboratory tests that will be performed at Visit 1 are:

- NT-proBNP

  NT-proBNP will be performed by the central lab in all patients at Visit 1.
- Thyroid stimulating hormone (TSH)
- Vitamin B12 and Folate
- Follicle stimulating hormone (FSH)

  FSH levels will be measured to confirm menopausal status in patients who have undergone oophorectomy without hysterectomy.

6.5.9 Pregnancy and assessments of fertility

Women of child bearing potential defined as all women physiologically capable of becoming pregnant are excluded. FSH levels, determined only in women who underwent oophorectomy without hysterectomy at Screening visit (Visit 1), should be in a range consistent with menopausal status for the patient to continue into the run-in period.

[redacted]

[redacted]

[redacted]

6.5.11 Appropriateness of safety measurements

Changes in amyloid accumulation as assessed by PET imaging are assessed as a safety endpoint in this study.

Amyloid PET imaging

A key secondary objective is to evaluate the effect of LCZ696 compared to valsartan on Aβ deposition in the brain assessed by PET imaging at 3 years. Changes in amyloid plaque deposition over time will be assessed using florbetapir ^{18}F. Longitudinal studies have demonstrated the usefulness of this tracer to detect changes in amyloid plaque load over a 2 year observation period in the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Chen et al 2015, Landau et al 2015). These data demonstrate that relevant changes in amyloid plaque deposition can be detected at 2 years using amyloid PET imaging (Villemagne et al 2011, Landau et al 2015) and that utilization of a cerebral white matter reference region may improve the power to track longitudinal changes in florbetapir ^{18}F (Chen et al 2015).

6.6 Other assessments

[redacted]

[redacted]

[redacted]

6.6.2 Resource utilization

Not applicable

6.6.3 Pharmacokinetics

Not applicable

[redacted]

[redacted]

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory tests, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patients and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Cognitive function test scores including the CogState battery [redacted] scale will not be communicated to the patients or sites routinely. Significant outlier scores will be flagged and the investigator will be notified. The investigator will ascertain if any unforeseen factors may have contributed to the outcome. An individual abnormal value on a cognitive scale by itself is not diagnostic of improvement or decline in cognitive function. The investigator should make appropriate decisions as to the need for further neuropsychological assessments at any time during the study based on clinical assessment irrespective of the cognitive scores. Results

[redacted]

of SUVr assessments on amyloid PET imaging and MRI volumetric assessments will not be communicated to the investigators. Patients who receive a diagnosis of MCI, dementia or stroke during the course of study may continue in the study.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- The severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment,
  - "No Relationship to study treatment or other investigational treatment" or
  - "Relationship to study treatment" or
  - "Relationship to other investigational treatment" or
  - "Relationship to both study treatment and other investigational treatment or indistinguishable"
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - see Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage increased/reduced
- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator

[redacted]

Notification (IN) or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of an SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E12D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E12D Guideline).

[redacted]

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period following the last administration of study treatment should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed. Liver events are divided into two categories:

- Liver events of special interest which consist of liver function test (LFT) elevations

[redacted]

- Medically significant liver events which are considered as SAEs and which consist of marked elevations of LFTs and / or pre-specified AEs.

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver events.

Any liver event which meets the criteria for "medically significant" event as outlined in Table 14-1 of Appendix 2 should follow the standard procedures for SAE reporting as described in Section 7.2.

Every liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

Details of monitoring and management of renal dysfunction are provided in Appendix 5.

7.5 Cognition safety monitoring

If dementia or dementia-related event occurs, the investigator will complete a Dementia-related Event form (provided by Novartis) in addition to the standard AE reporting. If a dementia or dementia-related event satisfies the definition of an SAE, the investigator must submit an SAE report in addition to the Questionnaire for the Dementia-related Event. Submission of a dementia report is not a substitution for the submission of an SAE report.

7.6 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA (European Medicines Agency) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an

[redacted]

AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE (Table 7-1).

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

AE – adverse event; eCRF – electronic case report form; SAE – serious adverse event

7.7 Pregnancy reporting

Given the age of the patient population and exclusion of women of child bearing potential no pregnancies are expected during the study. However, should a pregnancy be discovered during the course of study, the following procedure must be followed. In case of pregnancy discovered during the screening or run-in epochs or during double-blind epochs, the patient will be withdrawn from the study immediately.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

[redacted]

[redacted]

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA (clinical research associate) organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

[redacted]

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the clinical database system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff or Contract Research Organization (CRO) working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

CogState will provide cognitive battery data; imaging vendor will provide MRI and PET data. A selected vendor will provide [redacted] FAQ, [redacted] data electronically to Novartis. Each of these vendors will manage the database and these data will be generated electronically using a computer or tablet.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

[redacted]

[redacted]

8.4 Data Monitoring Committee

An external data monitoring committee (DMC) independent of Novartis will be appointed to monitor the study conduct and to review safety on a regular basis and determine if it is safe to continue the study according to the protocol. Any major recommendation from the DMC will be communicated to the Executive Committee and must be reviewed and ratified by the Executive Committee in consultation with Novartis prior to its enactment.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the "Data Monitoring Committee Charter". The DMC Charter will include information about data flow, purpose and timing of DMC meetings, guidance in the decision making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

In addition, the DMC charter will provide information about the composition of the committee and information about the scope of its mandate (e.g. which data will be reviewed, ability of the committee to request decoding of treatment codes, required reporting to Novartis, who has access to reports, actions planned in response to reports, or to make recommendations for changes in study conduct).

[redacted]

9 Data analysis

This section describes the planned approach to data analysis.

[redacted]

9.1 Analysis sets

The following analysis sets will be used for the statistical analyses:

- **Screened set (SCR)** – All patients who signed the informed consent. The screened set includes only unique screened patients, i.e., in the case of re-screened patients only the chronologically last screening data is counted.
- **Enrolled set (ENR) (run-in phase)** – All patients who received at least one dose of run-in study drug.
- **Valsartan run-in set (VRS)** – All patients who are in the ENR and received at least one dose of run-in valsartan.
- **LCZ696 run-in set (LRS)** – All patients who are in the ENR and received at least one dose of run-in LCZ696.
- **Randomized set (RAN)** – All patients who received a randomization number, regardless of receiving trial medication.
- **Full analysis set (FAS)** – it consists of all randomized patients with the exception of those patients who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization.
- **Safety set (SAF)** – it consists of all randomized patients who received at least one dose of study drug. Patients will be analyzed according to the treatment actually received. The safety population will be used for the analyses of safety variables.
- **Per-protocol set (PPS)** – it is a subset of the FAS which will consist of the patients who meet the following conditions:
  - No major deviations from the protocol procedures in the randomized treatment epoch
  - Have been exposed to study medication for at least 30 months and have 80% compliance on study medication.

Major protocol deviations will be pre-specified prior to unblinding treatment codes for analyses.

9.2 Patient demographics and other baseline characteristics

Unless specified otherwise, baseline value is defined as the measurement obtained at the randomization visit date (Day 1), or the measurement obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing.

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years), sex, race, ethnicity, country, region, weight, height, body mass index (BMI), education level, category of prior CV medication, prior HF hospitalization, NYHA class, NT-proBNP, vital signs, MMSE overall summary score, MMSE category (<28, ≥28), cerebrovascular disease burden factors as measured by MRI (e.g. lacunar infarcts > 2; cortical or subcortical infarct > 1cm^3; white matter lesion Fazekas score of 3; micro hemorrhages ≥4) and APOE4 allele status (carrier vs. non-carrier). BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (Screening Visit). Continuous variables will be

[redacted]

summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

Similar demographics and baseline characteristics will be also similarly summarized for patients participating in the PET imaging substudy. In addition, patients SUVr values, amyloid status (positive/negative), [redacted] at baseline will be summarized by treatment as well.

The Safety set will be the patient population for the above analyses.

9.3 Treatments

The overall duration on randomized study drug will be summarized by treatment group using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration category. Mean doses and dose levels will be summarized by treatment group and visit.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date respectively, will be summarized by therapeutic class, preferred term, and treatment group for the safety population.

The number and percentage of patients on treatments for AD or cognitive impairment will be tabulated by treatment group at baseline and during the randomized treatment epoch. Treatments for AD or cognitive impairment include glutamate receptor antagonists (memantine) and cholinesterase inhibitors (donepezil, galantamine, and rivastigmine).

The number and percentage of patients on different CV background medications (e.g., mineralocorticoid receptor antagonist, beta blockers, diuretics, and digoxin) will be tabulated by treatment at baseline and during the randomized treatment epoch.

The FAS will be used for the above analyses unless otherwise specified.

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

The primary variable is the change from baseline to 3 years in the CogState Global Cognitive Composite Score (GCCS). The CogState cognitive test battery includes the following seven tasks:

1. Detection Test (DET) – Assesses psychomotor function using the speed (milliseconds) of correct responses in a simple reaction time paradigm
2. Identification Test (IDT) – Assesses visual attention using the speed (milliseconds) of correct responses in a simple reaction time paradigm
3. Continuous Paired Associate Learning (CPAL) – Assesses visual episodic memory measuring accuracy of performance by the number of errors made over 6 learning trials
4. One back (ONB) - Assesses working memory using the speed (milliseconds) of correct responses in a n-back paradigm
5. International Shopping List Test (ISLT) – Assesses verbal learning using the accuracy (number of words recalled correctly) of recall in a verbal list learning paradigm

[redacted]

6. International Shopping List Test – delayed recall (ISLT-DR) - Assesses verbal memory using the accuracy (number of words recalled correctly) of delayed recall in a verbal list learning paradigm
7. Groton Maze learning Test (GMLT) – Assesses executive function using the number of total errors (number of error responses over 5 trials) in a hidden pathway maze learning paradigm

Standardized z-scores for each outcome measure and visit will be calculated using the sample baseline mean and standard deviation of individual tasks as follows:

- Z_{DET} = − (Log_{10}(DET) – baseline mean of log_{10}(DET))/SD of log_{10}(baseline DET),
- Z_{IDT} = − (Log_{10}(IDT) – baseline mean of log_{10}(IDT))/SD of log_{10}(baseline IDT),
- Z_{CPAL} = – (CPAL total errors – baseline mean of CPAL total errors/SD of baseline CPAL total errors),
- Z_{ONB} = − (Log_{10}(ONB) – baseline mean of log_{10}(ONB))/SD of log_{10}(baseline ONB),
- Z_{ISLT} = (ISLT – baseline mean of ISLT))/SD of baseline ISLT,
- $Z_{ISLT\text{-}DR}$ = (ISLT-DR) – baseline mean of ISLT-DR))/SD of baseline ISLT-DR,
- Z_{GMLT} = − (GMLT – baseline mean of GMLT))/SD of baseline GMLT

Note that negative sign is included in the calculation for tasks where increasing values indicate worsening performance (i.e., Z_{DET}, Z_{IDT}, Z_{ONB} and Z_{GMLT}) so that for all standardized change scores negative values indicate a decline from baseline while positive scores indicate improvement from baseline.

These seven individual z-scores are then combined to generate the GCCS:

CogState GCCS = average of (Z_{DET}, Z_{IDT}, Z_{CPAL}, Z_{ONB}, Z_{ISLT}, $Z_{ISLT\text{-}DR}$, Z_{GMLT})

The composite score will be computed if five of the seven tests are completed and the five tests provide an assessment of the three cognitive domains as defined below being assessed. That is, a composite score requires that each cognitive domain be measured by at least one cognitive test.

In addition to the GCCS, composite scores for three main subdomains memory, attention and psychomotor function will also be generated by combining the standardized change from baseline scores for individual tests from the CCB using the following formulae:

- Composite score of memory tests = average of (Z_{CPAL}, Z_{ISLT}, $Z_{ISLT\text{-}DR}$)
- Composite score of executive function tests = average of (Z_{ONB}, Z_{GMLT})
- Composite score of attention tests = average of (Z_{DECT}, Z_{IDT})

Each composite score will be the average of the non-missing individual test z-scores

9.4.2 Statistical model, hypothesis, and method of analysis

The change from baseline in the GCCS of CogState test battery will be analyzed using a repeated measures analysis of covariance (ANCOVA) model in which treatment, age stratification factor, MMSE stratification factor, education level, APOE4 status (carrier vs. non-carrier), baseline cerebrovascular disease burden as measured by MRI (calculated based on four factors: lacunar infarcts > 2; cortical or subcortical infarct > 1cm^3; white matter lesion

[redacted]

Fazekas score of 3; micro hemorrhages ≥4), visit (Weeks 26, 52, 78, 104, 130 and Week 156) and treatment-by-visit interaction are included as fixed-effect factors and baseline GCCS and visit by baseline GCCS interaction as covariates, with a common unstructured covariance matrix among visits between treatment group. The adjusted mean changes at 3 years (Week 156) within each treatment, the difference in mean changes at 3 years (Week 156) between the two treatments, and its 95% confidence interval obtained from the above model will be presented. In addition, the treatment difference (LCZ696-valsartan) in mean changes from baseline to 3 years will also be expressed based on a standardized effect size (Cohen's d) with a 2-sided 95% confidence interval. The Cohen's d will be estimated by using the adjusted between-treatment mean difference, divided by the estimated standard deviation, which is calculated from the standard error of the adjusted mean change and the sample number of patients within each group (the pooled SD) from the above modeling. The analysis is based on likelihood method with an assumption of missing at random (MAR) for missing data.

As the primary analysis, this repeated measure ANCOVA model will be performed in the Safety set including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment. The Cohen's d based on the adjusted difference in mean changes at 3 years (Week 156) between two treatments and its 95% confidence interval from this model will be used to draw the main conclusion for the primary objective. On-treatment data refer to cognitive test data collected while patients are on-study-medication (regardless of treatment interruption) or within three months after final study drug intake date.

In addition, the same repeated measure ANCOVA model will be performed in the following two analysis sets as supportive analyses:

- in the FAS, including all available data (even after treatment discontinuation and after start of treatments for AD or cognitive impairment)
- in the per-protocol set, including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment only.

Summaries of absolute values and change from baseline in the GCCS and domain-specific composite z-scores by treatment group and visit will be presented. Figures will be produced to visually show both the raw and the model-based mean global composite z-scores and mean domain-specific composite z-scores by visit over study period for each treatment group. These will be done in both the Safety and FAS with the same data inclusion rules as for the above repeated measure ANCOVA modeling in the Safety and FAS.

9.4.3 Handling of missing values/censoring/discontinuations

The repeated ANCOVA modeling as described in the previous section is based on likelihood method with an assumption of missing at random for missing data. That means, missing data, including those from dropouts, will be implicitly represented in the analysis by data from patients with similar baseline covariates and measurement histories.

Data collected more than three months after patients permanent discontinuation of the study medication will be excluded from analyses in both the Safety and PPS analyses. In addition, data collected after patients starting treatments for AD or cognitive impairment will be excluded from "on-treatment" analyses.

[redacted]

For missing values at a specific post-baseline visit, any post-baseline unscheduled measurements taken within three-month window may be re-mapped to this scheduled visit.

9.4.4 Sensitivity analyses

Although the MAR assumption is deemed appropriate choice for the primary analysis, it is not possible to verify its correctness based on the observed data (CHMP, 2010, National Research Council, 2010). Indeed it is conceivable that censoring, respectively the missing data mechanism (e.g., due to death) may be informative and that the cognitive function decline in patients who died would have been steeper than estimated under the MAR assumption. Thus, the primary analysis would favor the valsartan group in the presence of a reduction in mortality in the LCZ696 group.

Due to this uncertainty, analyses based on multiple imputations, such as those using a pattern mixture model approach, will be performed to investigate the sensitivity of the primary analysis results based on the MAR assumption. These sensitivity analyses assume that missing CogState test battery scores after death, HF hospitalizations, and stroke were missing not at random (MNAR).

Data censored at the start of treatments for AD or cognitive impairment may be imputed using similar MNAR-based imputation approach. This analysis will be performed for the primary analysis in the Safety set and for the supportive analysis in the FAS. In addition, a shared parameter model (Vonesh et al 2006) to jointly model longitudinal GCCS measurements and time to starting treatments for AD or cognitive impairment will be further explored. This provides an analysis of CogState test battery scores that accounts for potential informative censoring due to starting treatments for AD or cognitive impairment. It should be noted that this joint modeling approach might fail to work or interpretation of the results may be difficult if the incidence rate of patients starting treatment for AD or cognitive impairment in the present study is low.

To fully assess the effect of the missing data on the conclusions, an additional sensitivity analysis will be performed for subjects with missing cognitive function measurements due to withdrawal for unknown reasons.

In addition, the following subgroup analyses will be performed for the primary endpoint on the Safety set including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment. The analysis will be done using a similar repeated ANCOVA model as for the primary analysis at individual subgroup level separately, while the p-values of the subgroup-by-treatment interaction will be derived from a similar model but with additional terms including the subgroup, the interaction term of subgroup-by-treatment.

- Age group (<65 vs. ≥65 years), age group (<75 vs. ≥75 years)
- Gender (male/female)
- Region
- Education level
- Baseline MMSE cut-off (<28, ≥28)
- Baseline LVEF cut-off (<50%, ≥50%)
- Baseline NYHA class (II and III/IV)

[redacted]

- Baseline diabetes status (yes/no)
- Baseline cerebrovascular disease burden as measured by MRI
- APOE4 allele status (carrier/non-carrier)

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary variables are:

1. Change from baseline in individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the cognitive assessment battery at 3 years;
2. Change from baseline in the summary score of the instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) at 3 years.

The composite z-scores by individual cognitive domains (memory, executive function, and attention) are defined in Section 9.4.1.

For secondary variables composite z-scores by individual domain (memory, executive function and attention) and IADL, the changes from baseline to 3 years will be analyzed using the same repeated measures ANCOVA model as described in Section 9.4.2 but with baseline GCCS replaced with respective secondary variable baselines. The adjusted mean changes at 3 years (Week 156) within each treatment, the difference in mean changes at 3 years (Week 156) between two treatments, its 95% confidence interval obtained from the above model will be presented. The analysis is based on likelihood method with an assumption of missing at random for missing data, and will be performed in the Safety set including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment. On-treatment data are those collected while patients are on-study-medication (regardless of treatment interruption) or within three months after final study drug intake date. This analysis will be performed in the SAF.

In addition, as supportive analysis, similar repeated measure ANCOVA model will be also performed for these secondary endpoints for all data in the FAS.

Summaries of absolute values and change from baseline by treatment group and visit will be presented. Figures will be produced to visually show the endpoint values (SUVr, composite z-scores by cognitive domain and IADL) by visit over the study period for each treatment group. These analyses will be done in both SAF and FAS, for 'on-treatment' data and for all data, respectively.

For these secondary variables, a three month window will be applied to re-map any unscheduled visit assessments to a missing scheduled visit assessment.

9.5.2 Safety variables

Safety evaluations to be analyzed are listed as below:

- Change from baseline in a cortical composite SUVr (standardized uptake value ratio) at 3 years

[redacted]

[redacted]

Analysis on change from baseline in SUVr at 3 years

In order to make the most use of data collected from all available PET scan assessments, including the planned 'end-of-treatment' and 'end-of-study' assessments, the analysis of change from baseline (randomization) in a cortical composite SUVr at 3 years (Week 156) will be based on a model-based multiple imputation approach under MAR (missing at random) assumption.

The imputation model will include age stratification factor, MMSE stratification factor, region, baseline cerebrovascular disease burden as measured by MRI, APOE4 status (carrier vs non-carrier), and time (when the SUVr is assessed in days) as fixed effects with random intercept and slope (time) and a common unstructured covariance. This will be done separately within each treatment by baseline amyloid status (positive/negative). This imputation process will first create multiple imputations of missing SUVr at 3 years under a MAR assumption, resulting in multiple complete data sets after combining the imputed missing SUVr at 3 years values with the available SUVr at 3 years (so every patient with baseline SUVr in these multiple complete data sets have an SUVr value at 3 years).

An ANCOVA model using change from baseline to 3 years in SUVr as response variable, with treatment, age stratification factor, MMSE stratification factor, region, baseline cerebrovascular disease burden as measured by MRI, APOE4 status, baseline amyloid status as factors and baseline SUVr value as covariate will be run on each of these multiple completed data sets. Overall results and inference, including adjusted mean change at 3 years within each treatment, the difference in mean change at 3 years between two treatments, its 95% confidence interval, are obtained by applying Rubin's rules on the estimates obtained from the imputed/completed data sets.

As sensitivity analysis, the change in a cortical composite SUVr from baseline to 3 years will also be analyzed based on a repeated measures ANCOVA model in which treatment, age stratification factor, MMSE stratification factor, region, baseline cerebrovascular disease burden as measured by MRI, APOE4 status (carrier vs. non-carrier), baseline amyloid status (positive/negative), visit (18 months, 3 years), and treatment-by-visit interaction will be included as fixed-effect factors and baseline value and baseline-by treatment as covariates, with a common unstructured covariance matrix among visits between treatment group. The adjusted mean changes at 3 years (Week 156) within each treatment, the difference in mean changes at 3 years (Week 156) between two treatments, its 95% confidence interval obtained from the above model will be presented. The analysis is based on likelihood method with an assumption of missing at random for missing data. A three month window will be applied to re-map any unscheduled visit assessments to a missing scheduled visit assessment.

In addition, to assess the sensitivity of the MAR assumption used in multiple imputation, analyses based on multiple imputations, such as those using a pattern mixture model approach,

[redacted]

may be performed, which assumes that missing values after death, HF hospitalizations, stroke were missing not at random (MNAR).

A shift table to summarize the proportion of patients' amyloid status change over time from baseline by treatment will be provided as well.

All analyses will be performed in patients in the Safety set who participate in the PET image substudy, including 'on-treatment' data only. On-treatment data refer to the SUVr values obtained while patients are on-study-medication (regardless of treatment interruption) or within six months after final study drug intake date.

[redacted]

9.5.3 Resource utilization

Not applicable

9.5.4 Pharmacokinetics

Not Applicable

[redacted]

[redacted]

[redacted]

9.5.6 Biomarkers

For plasma Aβ1-40, the log-transformed ratio to baseline will be calculated for each subject at every post-dose time point, i.e. log (post-dose value/baseline). The change from baseline to a pre-defined time-point (Weeks 13, 52, 104 and 156) in logarithmic scale will be analyzed using the same repeated measures ANCOVA model as for the primary endpoint but with baseline GCCS replaced with baseline biomarker values in logarithmic scale. The adjusted mean changes at each visit within each treatment, the difference in mean changes between two treatments, its 95% confidence interval obtained from the above model will be provided. These estimates and confidence intervals will be back-transformed for presentation.

Summaries of absolute values and change from baseline in Aβ1-40 by treatment group and visit will be presented using statistics: n, mean, SD, median, minimum, maximum, Q1, Q3, geometric mean and Coefficient of Variation. Figures will be produced to visually show the mean Aβ1-40 levels by visit over study period for each treatment group.

All of the above analyses will be performed for patients for whom the biomarker data is obtained in the Full analysis set including all data.

9.5.7 PK/PD

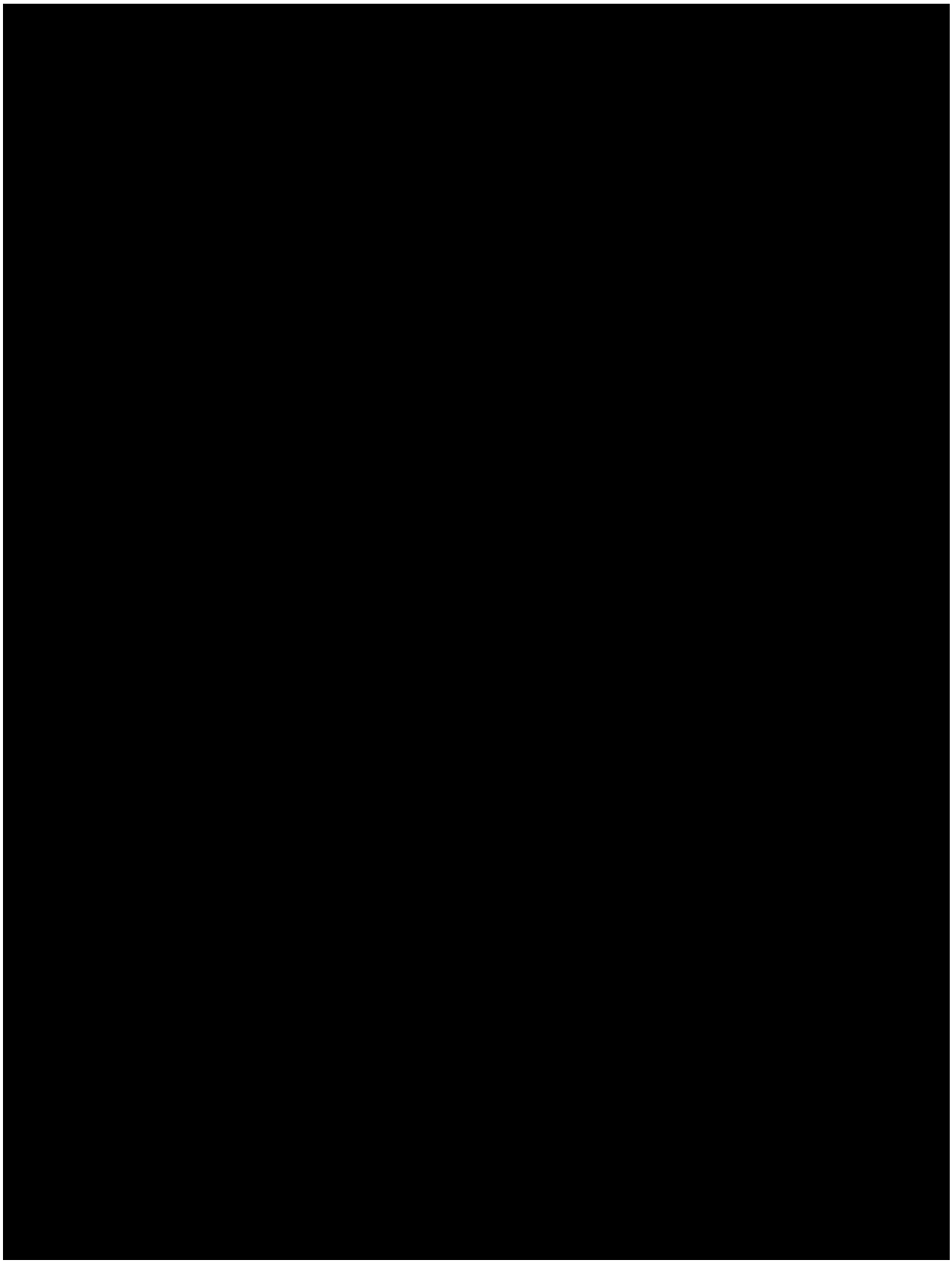
Not applicable

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

9.7 Interim analyses

No formal interim efficacy analyses are planned. Refer to Section 8.4 for planned regular interim safety data review by an independent Data Monitoring Committee.

9.8 Sample size calculation

9.8.1 Sample size calculation for the primary endpoint

It is currently estimated that approximately 180 patients per group

- would provide at least 80% probability that the 2-sided 95% confidence interval (CI) excludes a standardized effect size (Cohen's d) of 0.3 (or greater) in change in composite z-score of the battery test over 3 years, given that there is no expected difference between two treatments.
- Would provide at least 80% probability that the 2-sided CI excludes 0 (corresponding to $p<0.05$), if the true effect size is 0.3 or greater (in either direction).

An effect size of 0.3 in Cohen's d corresponds to a margin of 0.3xSD (SD=standard deviation) on the original scale for the difference between treatments in mean global score change from baseline, and is generally considered as small (Cohen 1988). In a systematic review of studies for health-related quality of life instruments that have reported the minimally important difference (MID), it was found that for the majority of studies the MID estimates were consistently close to 0.5xSD (Norman et al 2003). In addition, socially accepted benchmarks for conditions that induce cognitive impairment such as low level alcohol intoxication within legal driving limit in most countries (0.05%) are generally associated with declines of 0.3 or higher for psychomotor speed, attention and working memory. Therefore, the sample size of the study was determined to be able to detect (or exclude) effect sizes in the magnitude of 0.3 in Cohen's d with high probability, as it appears to be an appropriate choice to guide the interpretation of the cognitive function results.

In addition, defining the magnitude of the MID using a measure of effect size, rather than a raw difference score has additional advantages:

- Expressing the magnitude of an important difference in scale free units (Cohen's d) allows models of clinically meaningful difference to be based on integration of outcomes from a broad set of studies whose characteristics are relevant to the current study (i.e. magnitude of change in cognition related to amyloid, magnitude of change occurring after heart failure, and magnitude of change related to cardiovascular disease).
- Estimates of clinically meaningful difference can be referenced to the magnitude of cognitive decline detected from studies where compounds with accepted central nervous system adverse effects, at known doses are administered to older adults (e.g. scopolamine, alprazolam).

Sample size calculation was performed using N-Query 7.0.

9.8.2 Sample size calculation for the PET imaging substudy

Approximately 300 patients (in 1:1 allocation ratio to LCZ696 and valsartan) will provide at least 80% probability that the 2-sided 95% CI excludes a between-treatment absolute

[redacted]

difference of 0.01 (corresponding to an incremental 33% increase in LCZ696 vs. valsartan) in change from baseline in SUVr over 3 years if there is no expected difference between two treatments. This calculation is based on the assumptions that the mean change over 3 years from baseline in SUVr is 0.03 in the control group, the common standard deviation is 0.03 (estimated from ADNI data, Chen et al 2015). It is noted that the ADNI data presented in Chen's paper are by patients' cognitive status (normal, MCI, dementia) and for changes over two years. The assumptions used here are guestimates from the 2 year data in normal cognitive and MCI subjects.

An absolute difference in SUV ratio of 0.01 was considered small as it represents a value that is lower than the rate of SUVr change that distinguishes between amyloid positive and negative patients (0.026 vs. 0.011).

Sample size calculation was performed using N-Query 7.0.

9.8.3 Blinded sample size re-estimation

Approximately 520 patients will be randomized in order to provide overage to account for the information loss caused by an estimated 30% "drop-out" (including death, lost-to-follow-up, permanent discontinuation of study medication and start of treatments for AD or cognitive impairment) during 3 year period. In the PET imaging substudy approximately 430 patients will be randomized.

A loss of 30% of information is a crude estimate therefore it is planned to monitor the 'drop-out' pattern as the trial is ongoing in order to provide a better prediction of the information loss for a given number of patients. The final number of patients randomized may be reduced if there is sufficient evidence that the information loss will be less than 30% and that the precision of the estimates of treatment effect (as described in the sample size section above), will be maintained.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. He/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

[redacted]

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

[redacted]

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality control and quality assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

[redacted]

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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14 Appendix 2: Liver event definition and follow-up requirements

Table 14-1 Liver event definitions

	Definition/ threshold
AE of special interest Laboratory values	• ALT or AST > 3 x ULN • ALP > 2 x ULN • TBL > 1.5 x ULN
Medically significant event (SAE) Laboratory values	• ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) • ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) • TBL > 3 x ULN • Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN
AEs	• Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow up requirements for liver events

Criteria	Event type	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST			
> 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for more than 2 weeks, discontinue the study drug Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms[b]	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator

[redacted]

Criteria	Event type	Actions required	Follow-up monitoring
		Establish causality	discretion)
> 3 to ≤ 5 x ULN (patient is asymptomatic)	Adverse event of special interest (AESI)	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 3 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE Establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
> 2 to ≤5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week. If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 3 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Novartis Repeat LFT once or twice in the week. If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			
Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
"Drug-related hepatic disorders - severe events only" SMQ AE	Medically significant	Discontinue the study drug Hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality	Investigator discretion

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

[b] General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

[redacted]

15 Appendix 3: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.3 mmol/L [mEq/L])

General principles

Elevation of potassium levels above the predefined values should be repeated and confirmed before any action is taken.

Any patient with a serum potassium > 5.3 mmol/L (mEq/L) at any time after randomization requires the Investigator to confirm the potassium concentration in a non-hemolyzed sample via an immediate repeat lab sample to both the clinic local lab and the study central lab. Regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) should continue until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L [mEq/L]) or potential danger (≥ 6.0 mmol/L [mEq/L]).

Patients with elevated potassium value will be managed according to the corrective actions outlined below. Hyperkalemia should be followed until resolution.

Corrective action for management of hyperkalemia

Serum potassium greater than 5.3 and less than or equal to 5.5 mmol/L (mEq/L)

- Confirm potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g., orange juice, melon, bananas, tomatoes, dried fruits, potatoes, low-salt substitutes, tomatoes, coffee, etc.)
- Correct metabolic acidosis if necessary.
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
    1. MRAs (if they are believed to be the most likely cause of hyperkalemia)
    2. Potassium-sparing diuretics (e.g., amiloride and triamterene) including in combination products with thiazide or loop diuretics
    3. Potassium supplements, e.g., potassium chloride
    4. Salt substitutes
    5. Non-steroidal anti-inflammatory drugs (NSAIDs)
    6. Cyclo-oxygenase-2 (COX-2) inhibitors
    7. Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
    8. Herbal Supplements:
       For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries

[redacted]

- Assess patient for dehydration or any condition that could lead to dehydration (e.g., diarrhea, vomiting) and/or hypovolemia and initiate appropriate corrective measures of rehydration.
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains > 5.3 and ≤ 5.5 mmol/L (mEq/L), regularly monitor serum potassium levels to ensure stability (suggested once monthly)
- Consider down-titration of study drug, according to investigator's medical judgment.

Serum potassium greater than 5.5 and less than 6.0 mmol/L (mEq/L)

- Confirm potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- Apply all measures outlined for serum potassium > 5.3 and ≤ 5.5 mmol/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

Serum potassium greater than or equal to 6.0 mmol/L (mEq/L)

- Immediately discontinue study drug
- Confirm potassium concentration in a non-hemolyzed sample
- Urgently evaluate patient and treat hyperkalemia as clinically indicated
- Apply all measures outlined for serum potassium > 5.3 and < 6.0 mmol/L (mEq/L)

No resumption of study drug without individualized case discussion with and permission from Novartis medical monitor or his/her designee.

[redacted]

16 Appendix 4: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor BP closely
2. If symptomatic hypotension occurs:
   a. Correct any treatable cause, e.g. hypovolemia
   b. If hypotension persists, any antihypertensive drug such as diuretics, calcium channel blockers (CCBs), nitrates, beta blockers, aldosterone antagonists and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered. Any non-antihypertensive drug (such as nitrates) should be considered for down-titration prior to study drug as determined by the best judgment of the investigator.
   c. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 5.5.5 should be adhered to as much as possible.

[redacted]

17 Appendix 5: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by either study drug. Moreover, renal dysfunction may develop or may deteriorate in some patients after study drug administration. These recommendations have been developed to guide the investigators in managing patients with renal dysfunction after randomization.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥25% from baseline (Visit 1) (or if serum creatinine concentration increase to 2.5 mg/dL [221 μmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect creatinine
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study drug

Action situation

If a patient's eGFR decreases by ≥40% from baseline (Visit 1) (or if serum creatinine concentration rises above 3 mg/dL (265 μmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above).

The investigator may consider down-titration of study drug. If the investigator judges that study drug has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study drug was stopped, every effort will be done to restart it again, according to clinical conditions.

[redacted]